Virtual reality exposure therapy as treatment for pain catastrophizing in Fibromyalgia patients: Proof-of-concept

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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety of in part submitted it for obtaining any qualification.

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ABSTRACT

Research objective

To test a novel concept that exposing patients with fibromyalgia syndrome (FMS) to visuals of exercise activities elicits neurophysiological changes in functional brain areas associated with pain catastrophization; thereby providing preliminary support for the further development/testing of a virtual reality exposure therapy (VRET) exercise program aimed at reducing pain catastrophization toward exercise therapy in patients with FMS.

Methods

The main study of this research consisted of a three-phase exploratory fMRI study. Phase 1 involved the development/validation of the fMRI visual task. Phase 2 involved the exploration of the differences in neural correlates associated with pain catastrophizing between participants with FMS and healthy controls when exposed to various visuals of exercise and passive/relaxing activities. Phase 3 involved the testing of the preliminary efficacy of a novel VRET exercise program on pain catastrophization in participants with FMS. The fMRI task consisted of two stimuli: active (exercise activity visuals)/passive (relaxing activity visuals). Structural images as well as blood-oxygenation-level-dependent (BOLD) contrasts were acquired for the conditions and compared within-subjects/groups and between-groups. The condition of interest was the active>passive condition (where brain activations for the passive condition were subtracted from the active condition). The brain volumes collected during 'on' conditions were compared with the brain volumes collected during 'off' conditions using Students' *t test*. Statistic images were thresholded using clusters determined by $Z>2.3$ and a (corrected) cluster significance threshold of $p=0.05$.

Results

The *right (R) middle and inferior frontal gyrus* and *R posterior cerebellum* were significantly activated for the participants with FMS, and not the healthy control group, during the active>passive condition (phase 2). At baseline, during the active>passive condition (phase 3), the intervention/VRET group showed significant activation (p<0.05) in the *R insular cortex, R anterior and posterior cerebellum, R parahippocampal gyrus, R middle frontal gyrus, R corpus callosum, R thalamus, R supramarginal gyrus* and *R middle and superior temporal gyrus*; the control group showed significant activation in the *R anterior and posterior cerebellum, R middle and superior temporal gyrus, R middle frontal gyrus, R insular cortex, R supramarginal gyrus* and *R precentral gyrus*. Post-intervention, during the active>passive condition, *R posterior cerebellum* activation was still significant (p<0.05) for the intervention group; *R anterior cerebellum, left (L) middle and inferior frontal gyrus,* and *R superior parietal lobe* activation was found to be significant (p<0.000) for the control group, although these areas were not found to be significantly activated at baseline for the control group.

Conclusion

We could not provide confirmatory evidence for the efficacy of a novel VRET program for pain catastrophization in patients with FMS. However, the findings of this study does suggest that pain catastrophization in patients with FMS could be confirmed with fMRI. Research is therefore warranted to further develop a proper VRET exercise program and to test the effect of this program on pain catastrophization in patients with FMS.

Key words: *fibromyalgia syndrome, pain catastrophizing/catastrophization, virtual reality exposure therapy, exercise, compliance, fMRI*

ABSTRAK

Navorsing doelstelling

Om 'n nuwe konsep dat die blootstelling van pasiënte met fibromialgie sindroom (FMS) aan beeldmateriaal van oefening, ontlok neurofisiologiese veranderinge in funksionele brein-areas wat verband hou met pyn katastrofering te toets; sodoende voorlopige steun vir die verdere ontwikkeling/toetsing van 'n virtuele realiteit blootstelling terapie (VRET) oefenprogram wat gemik is op die vermindering van pyn katastrofering na oefenterapie in pasiënte met die FMS te bied.

Metodes

Die hoofstudie van hierdie navorsing bestaan uit 'n drie-fase verkennende fMRI studie. Fase 1 het die ontwikkeling/validering van die fMRI visuele taak behels. Fase 2 het die ondersoek van die verskille in die neurale korrelate geassosieer met pyn katastrofering tussen deelnemers met FMS en gesonde kontroles wanneer hulle blootgestel word aan verskeie beeldmateriaal van oefening en passiewe/ontspannende aktiwiteite behels. Fase 3 het die toets van die voorlopige effektiwiteit van 'n nuwe VRET oefenprogram op pyn katastrofering in deelnemers met FMS behels. Die fMRI taak het bestaan uit twee stimuli: aktiewe (oefening aktiwiteit beeldmateriaal)/passiewe (ontspannende aktiwiteit beeldmateriaal). Strukturele beelde sowel as bloed-suurstof-vlak-afhanklike (BSVA) kontraste is vir die toestande verkry en vergelyk binne-deelnemers/groepe en tussen-groepe. Die toestand van belang was die aktiewe>passiewe toestand (waar brein aktivering vir die passiewe toestand afgetrek is van die aktiewe toestand). Die brein volumes wat ingesamel tydens die 'aan' toestande is vergelyk met die brein volumes wat ingesamel is gedurende die 'af' toestande met die gebruik van Studente se *t-toets*. Drempel statistiek beelde is gegroepeer deur Z> 2,3 en 'n (gekorrigeerde) groepeerde betekenisvolle drempel van p = 0.05.

Resultate

Die regter *(R) middel- en inferior-frontale gyrus* en *R posterior serebellum* is betekenisvol geaktiveer vir die deelnemers met FMS, maar nie vir die gesonde kontrole groep nie, gedurende die aktiewe>passiewe toestand (fase 2). By basislyn, tydens die aktiewe>passiewe toestand (fase 3), die intervensie / VRET groep het betekenisvolle aktivering ($p < 0.05$) in die *R insulaire korteks, R anterior en posterior serebellum, R para-hippokampus gyrus, R middel-frontale gyrus, R korpus kallosum, R talamus, R supramarginale gyrus* en *R middel- en superior-temporale gyrus*; die kontrole groep het betekenisvolle aktivering in die *R anterior en posterior serebellum, R middel- en superior-temporale gyrus, R middel-frontale gyrus, R insulaire korteks, R supramarginale gyrus* en *R presentrale gyrus*. Post-intervensie, tydens die aktiewe>passiewe toestand, was *R posterior serebellum* aktivering betekenisvol ($p < 0.05$) vir die intervensie groep; *R anterior serebellum, links (L) middel- en inferior-frontale gyrus* en *R superior pariëtale lob* aktivering was betekenisvol ($p < 0.000$) vir die kontrole groep, alhoewel geen betekenisvolle basislyn aktivering in hierdie areas by die kontrole groep plaasgevind het nie.

Gevolgtrekking

Ons kan nie bewyse vir die effektiwiteit van 'n nuwe VRET program vir pyn katastrofering in pasiënte met FMS bevestig nie. Nietemin, dui die bevindinge van hierdie studie wel daarop dat pyn katastrofering in pasiënte met FMS bevestig kon word met fMRI. Verdere navorsing is dus geregverdig om 'n behoorlike VRET oefenprogram te ontwikkel en die uitwerking van hierdie program op pyn katastrofering in pasiënte met FMS te toets.

Sleutel woorde: *fibromialgie sindroom, pyn katastrofering, virtuele realiteit blootstelling terapie, oefening, nakoming, fMRI*

CONTENTS

DEDICATION

Dedicated to:

The Lord God, Almighty
My loving and supportive parents, Glenda and Cedric Morris
My devoted and patient husband, Grant
My beautiful and understanding daughter, Georgia
My supportive sisters, Lucinda and Letitia,
and
My best friend, who kept me sane, Amanda

Without your support and love, none of this would have been possible…

In loving memory of my grandmother, Mamma.

Missing you dearly.

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GLOSSARY

Acronyms

- **ACR** – American College of Rheumatology
- **BOLD** – Blood Oxygen Level Dependent
- **CBT** – Cognitive-Behavioural Therapy
- **CI** – Confidence intervals
- **CPE** – Committee of Postgraduate Education
- **CUBIC** – Cape Universities Brain Imaging Centre
- **FIQR** – Revised Fibromyalgia Impact Questionnaire
- **fMRI** – Functional Magnetic Resonance Imaging
- **FMS** – Fibromyalgia syndrome
- **GPPAQ** – General Practice Physical Activity questionnaire
- **HMD** – Head-mount display
- **ICC** – Intraclass correlation coefficient
- **MD** – Mean difference
- **MDC** – Minimal detectable change
- **OM** – Outcome measure
- **OMTs** – Outcome measurement tools
- **PCS** – Pain Catastrophizing Scale
- **SA** – South Africa
- **SA-FIQR** – South African revised Fibromyalgia Impact Questionnaire
- **SA-PCS** – South African Pain Catastrophizing Scale
- **SA-TSK** – South African Tampa scale for Kinesiophobia
- **SD** – Standard deviation
- **SEM** – Standard error of measurement
- **SU** – Stellenbosch University
- **TSK** – Tampa Scale for Kinesiophobia
- **TBH** – Tygerberg Hospital
- **UCT** – University of Cape Town
- **VR** – Virtual Reality
- **VRET** – Virtual Reality Exposure Therapy

Definition of terms

- **Adherence:** the extent to which the patient continues the agreed-upon mode of treatment under limited supervision when faced with conflicting demands, as distinguished from compliance or maintenance (http://medical-dictionary.thefreedictionary.com/adherence).
- **Adult:** a person grown to full size and strength; one who has reached maturity; an individual aged 18 years and older (http://dict.die.net/adult/).
- **Allodynia:** is pain due to a stimulus which does not normally provoke pain; commonly witnessed in patients with fibromyalgia syndrome (Merskey et al., 1994).
- **Blood oxygen level dependent (BOLD):** a functional magnetic resonance imaging (fMRI) technique that utilizes the differences in magnetic susceptibility between oxyhaemoglobin and deoxyhaemoglobin to acquire images of areas activated in the brain (Westbrook., 2010; pg 125).
- **Cronbach's alpha (α):** indicates the strength of the relationship between all the items on an outcome measurement tool (Osman et al., 2000).
- **Cognitive-behavioural therapy (CBT):** a generic term which incorporates a wide range of treatment modalities (i.e. stress management, distraction, relaxation, problem-solving, cognitive restructuring), all of which are designed to educate the patient and enhance coping, facilitate self-management, improve function and teach the patient to use cognitive techniques to recognize and change negative cognitions (Burckhardt et al., 2005).
- **Content validity:** "the extent to which each item/question in an instrument accurately measures the desired information" (Portney et al., 2000).
- **Cross-sectional convergent validity:** "the extent to which the scores of the outcome measurement of interest relate to other measures in an expected manner" (DeVon et al., 2007).
- **Exposure therapy:** a technique that involves exposing an individual to a task or movement that he/she fears until the emotion of fear is alleviated and disassociated from that particular task or movement (Vlaeyen et al., 2001).
- **Face validity: "**indicates that an instrument appears to test what it is supposed to and that it is a plausible method for doing so" (Portney et al., 2000; pg 82).
- **Fear-avoidance behaviours:** a specific fear of a movement or task, based on the belief that it will result in (re)injury and pain (Leeuw et al., 2007). Also known as 'Kinesiophobia'.
- **Fibromyalgia syndrome (FMS):** a chronic, non-inflammatory and non-articular rheumatologic syndrome characterized by widespread musculoskeletal pain, decreased function, allodynia, hypersensitivity to palpation of specific body locations, fatigue, sleep disturbances, anxiety, activity avoidance behaviours and psychological disturbances (Williams et al., 2009). Other symptoms could include occipital headaches, morning stiffness, digital paresthesia/numbness, chest wall pains, irritable bowel and irritable bladder syndromes (Peterson et al., 2007).

- **Functional magnetic resonance imaging (fMRI):** a medical imaging technique which provides high resolution, non-invasive reports of neural activity detected by blood oxygen level dependent (BOLD) signals (Nebel et al., 2009).
- **Internal consistency:** measures how consistent the scores of an instrument are within itself (Portney et al., 2000).
- **Intraclass coefficient correlation:** "an index of the reliability of the measurements between tests" (Müller et al., 1994).
- **Minimal detectable change:** "the degree of change required in an individual's score to ascertain if the change is real, over and above measurement error" (Monticone et al., 2011).
- **Pain catastrophizing:** a cognitive strategy, broadly defined as an exaggerated negative orientation towards actual or anticipated pain experiences (Sullivan et al., 1995).
- **Patient compliance:** the degree or extent to which a patient follows or completes a prescribed diagnostic, treatment, or preventive procedure (http://medical-dictionary.thefreedictionary.com/Patient+compliance).
- **Proof-of-concept study:** represents an area of research that is an ideal target for innovative designs. Proof-of-concept studies are carried out to determine if there is early evidence of clinical efficacy using a small, targeted number of subjects, to warrant taking a drug or an intervention further in development (Leung et al., 2006).
- **Sensitivity-to-change:** "the capacity of a measure to detect change in patients over time" and relates to the "clinical meaningfulness of changes in scores" (Stratford et al., 1998; Riddle et al., 1998).
- **Standard error of measurement:** estimates how repeated measures on the same instrument tend to be distributed around the "true" score (Brown et al., 1999).
- **Test-retest reliability:** The degree to which an instrument is stable based on repeated administrations of the test to the same individuals over a specified period of time (Portney et al., 2000; pg 752).
- **Virtual reality (VR):** a technology which allows a user to interact with a computer-stimulated environment, be it real or imagined. Virtual reality environments are primarily visual experiences, displayed either on a computer screen or through special stereoscopic displays, head-mount display, but some simulations include additional sensory information, such as sound through speakers or headphones. Users can interact with the environment via an input device such as a mouse, joystick or keyboard (Powers et al., 2008).
- **Virtual reality exposure therapy (VRET)**: the conduction/delivery of exposure therapy via a virtual reality system (Powers et al., 2008; Parsons et al., 2008).

“Change your thoughts and you change your world.”

Norman Vincent Peale

OVERVIEW OF THESIS

The following diagram provides an overview of the chapters presented in this thesis:

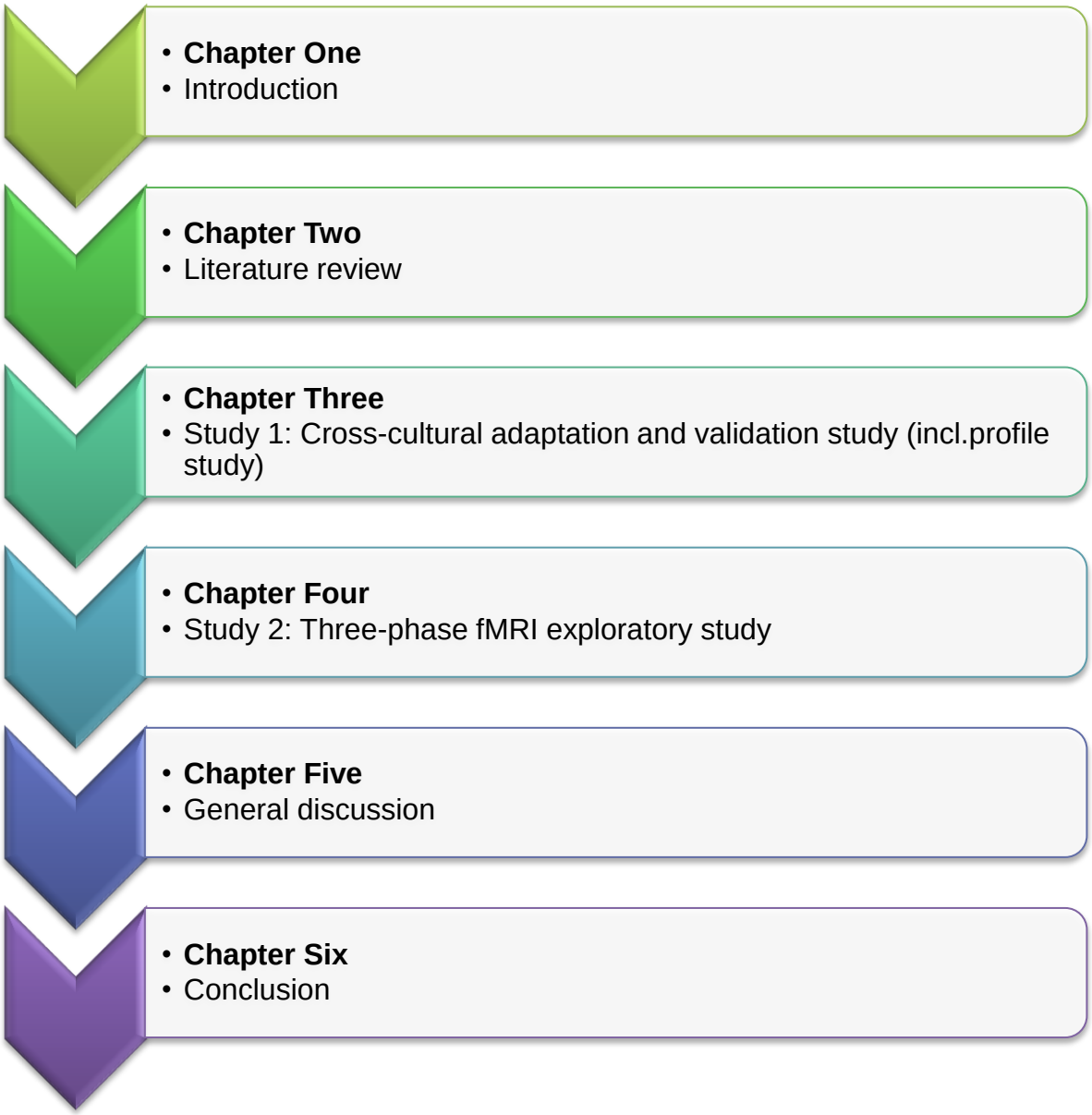


Figure 1: Overview of thesis chapter layout

CHAPTER ONE

INTRODUCTION

1.1 Background

Fibromyalgia syndrome (FMS), a non-inflammatory and non-articular rheumatologic condition, is arguably one of the most complex chronic pain conditions to treat (Goldenburg., 2008; Buskila et al., 2009; Wurtman et al., 2010). Primarily characterized by persistent widespread pain, hypersensitivity on palpation/allodynia, chronic fatigue and functional disability (Spaeth., 2009; Clauw et al., 2009); FMS remains a mysterious condition (Peterson et al., 2007). Although a number of theories have been postulated for possible causes of FMS ranging from physiological to psychological parameters; none have been found to provide a comprehensive causal explanation for FMS (Peterson et al., 2007; Bradley et al., 2008). The ambiguities surrounding the aetiology of FMS have therefore led to a number of controversial opinions as to whether or not FMS is an actual or legitimate disease (Wallace et al., 2001; Hazemeijer et al., 2003; Peterson et al., 2007). Nonetheless, symptoms which are described as FMS continues to disable millions around the globe and incur significant costs to healthcare and industrial sectors annually (Sicras-Mainar et al., 2009); equally frustrating health professionals and intriguing researchers (Peterson et al., 2007).

The inability to identify an exact aetiology for FMS has resulted in the current management of FMS largely being based on symptomatic relief (Buskila et al., 2009). Generally, FMS management programs consist of a combination of pharmacological and non-pharmacological therapies (Boomershine et al., 2009; Sarzi-Puttini et al., 2008). Although no one treatment strategy has been found to be superior, there is consistency in evidence from meta-analyses and clinical practice guidelines strongly indicating that exercise therapy should form a key component in the management of FMS (Brosseau et al., 2008; Williams et

al., 2009; Thomas et al., 2010; Kelley et al., 2010; Kelley et al., 2011). To date, exercise therapy has been shown to significantly reduce functional disability and symptoms in FMS (Jones et al., 2009; Williams et al., 2009; Thomas et al., 2010; Kelley et al., 2011), and is currently the most advocated management strategy for FMS in physiotherapy practices (Kelley et al., 2010; Haüser et al., 2011).

The implementation of exercise therapy as a management strategy for FMS in practice is, however, significantly hampered by poor compliance to exercise programs often displayed among patients with FMS (Richards et al., 2002; Oliver et al., 2002; Busch et al., 2008; Jones et al., 2009; Ablin et al., 2010; Gowans et al., 2010). A key predictor of poor compliance in FMS has recently been identified as *pain catastrophization*, a cognitive strategy, broadly defined as "*an exaggerated negative orientation towards actual or anticipated pain experiences"* which significantly contributes to the maintenance of pain (Sullivan et al., 1995; Hassett et al., 2000; Edwards et al., 2006; Quartana et al., 2009; Börsbo et al., 2010). Currently, the role of pain catastrophization is believed to be more pronounced in FMS than in other rheumatologic chronic pain condition and is recognized as a barrier to the healthy re-establishment of psychological and physical functioning among patients with FMS (Hassett et al., 2000; Edwards et al., 2006; Rodero et al., 2008; Quartana et al., 2009; Börsbo et al., 2010). Of concern is that in patients with FMS, the presence of pain catastrophization leads to fear-avoidance behaviours which often result in attrition from regular physical activity (Hassett et al., 2000). Inactivity is particularly detrimental in FMS and typically leads to further complications such as deconditioning of the musculoskeletal system, increased pain, increased fatigue and functional disability (Oliver et al., 2002; Jones et al., 2009; Börsbo et al., 2010). Fundamentally, poor compliance towards exercise and physical activity among patients with FMS is the primary factor contributing to the chronicity and accelerated deterioration of the condition (Ablin et al., 2010).

Although research remains primarily focused on identifying the aetiology of FMS and on finding effective management strategies for FMS symptoms (Peterson et al., 2007); over the past two decades, focus in research has shifted. Researchers are now trying to identify predictors of poor treatment compliance in FMS and to find effective interventions which could improve compliance toward management strategies such as exercise therapy among patients with FMS (Huyser et al., 1997; Oliver et al., 2002; Dobkin et al., 2005; Dobkin et al., 2006; Dobkin et al., 2008). Reasons for this mind-shift in research can be attributed to the fact that although effective management strategies such as exercise therapy for FMS symptoms may exist; their value in clinical practice is often diminished due to poor patient compliance (Cameron et al., 1995; Jones et al., 2009; Thomas et al., 2010; Gowans et al., 2010). Furthermore, the high rates of subjects lost to follow-up in many FMS exercise clinical trials due to non-compliance, is concerning since the outcomes of the studies could largely be affected (Dobkin et al., 2005; Jones et al., 2009). Strategies to increase compliance to effective treatment strategies such as exercise therapy in FMS are therefore warranted.

To our knowledge, there is a dearth of research into the actual management approaches aimed at addressing poor compliance towards prescribed exercise programs in FMS. The inference that pain catastrophization and subsequent fear-avoidance behaviours may influence the compliance of patients with FMS toward exercise programs, justifies finding treatment approaches to alter pain catastrophization in the management of FMS (Garcia-Campayo et al., 2009; van Koulil et al., 2007). It is therefore postulated that by reducing pain catastrophization in patients with FMS, fear of movement would be decreased, compliance towards exercise therapy would be increased and the real physiological and psychological benefits of exercise therapy for patients with FMS would be realized.

Empirical evidence suggests that cognitive-behavioural therapy (CBT), specifically exposure therapy, may be useful in the alteration of pain catastrophization observed in patients with FMS (Rodero et al., 2008). Traditionally, exposure therapy is conducted during real

situations (in vivo exposure therapy) or during an imagined situation (imagined exposure therapy). However, more recent innovations indicate that exposure therapy may also be administered via virtual reality technology, namely *virtual reality exposure therapy (VRET)* or in virtuo exposure therapy (Parson et al., 2008; Powers et al., 2008). VRET is a type of exposure therapy in which the user can be immersed into a computer-generated environment via a head-mount display and be visually exposed to a simulation of a specific feared situation (Parson et al., 2008; Powers et al., 2008; Bush et al., 2008). Contrary to other types of exposure therapy, VRET seems ideal for conditions where the real situations are inaccessible or costly (in vivo exposure) or individuals find it difficult to imagine various situations (imagined exposure therapy) (Parson et al., 2008; Powers et al., 2008). To date, VRET has successfully been used for a variety of phobias, such as fear for spiders and flying (Parson et al., 2008; Powers et al., 2008; Bush et al., 2008), but has never been used in the treatment of fear of movement/exercise, nor for pain catastrophizing in chronic pain conditions.

1.2 What is this research about?

That imagined exposure therapy may effectively reduce pain catastrophizing in patients with FMS (Rodero et al., 2008), makes the investigation of a novel VRET exercise program as a possible treatment option for pain catastrophizing in FMS, plausible. However, since there is no available VRET exercise program for the treatment of pain catastrophizing in patients with FMS; preliminary steps were required prior to the further development and testing of such a program. Initially, it had to be ascertained if visual exposure to catastrophized exercise activities cognitively triggered functional brain areas associated with pain catastrophizing in patients with FMS. The premise was that if visual stimuli of the catastrophized exercise activities cognitively triggered pain catastrophization in previously identified functional brain areas of patients with FMS (Gracely et al., 2004); a VRET program aimed at exposing patients with FMS to visuals of the feared or catastrophized exercises and neutralizing feelings of catastrophization towards exercise activities, could possibly

decrease pain catastrophizing and subsequently decrease fear of movement. In turn, compliance towards prescribed exercise programs in clinical practice may be increased.

The research presented in this thesis was therefore primarily aimed at testing the novel concept that exposing patients with FMS (who catastrophized pain related to exercise), to healthy exercise activities presented via visuals elicits neurophysiological changes in functional brain areas associated with pain catastrophization which would in turn provide preliminary support for the further development and testing of a specifically-designed VRET program aimed at reducing pain catastrophization toward exercise therapy in patients with FMS.

1.3 Significance of this research

Non-compliance towards prescribed exercise programs is typically observed among FMS populations (Huyser et al., 1997; Oliver et al., 2002; Dobkin et al., 2005; Dobkin et al., 2006; Dobkin et al., 2008; Jones et al., 2009). Many factors have been identified as key role players in the development of non-compliance, of which cognitive behavioural strategies seemed to be particularly influential (Oliver et al., 2002; Dobkin et al., 2005; Dobkin et al., 2006a; Dobkin et al., 2006b). The identification of the role that cognitive behavioural strategies (such as pain catastrophization) have in the development of fear-avoidance behaviours and attrition from physical activity; warrants targeting pain catastrophization in the management of FMS (Hassett et al., 2000). Over the past two decades, there has been an increase in the use of psychological treatments such as CBT in the physiotherapy practice (Everett et al., 1995 as cited in French., 1997; pg 421). According to the Chartered Society of Physiotherapy in 1991, physiotherapists "*must be skilled … to prevent, cure or alleviate physical manifestations of somatic and psychological disease*." Despite this recommendation, the physiotherapy practice continues to be primarily focused on the physical and physiological factors of a condition. Physiotherapists may be aware of the

psychological barriers to management displayed by FMS and other patients, but may not feel adequately skilled or prepared to deal with these issues in practice (French et al., 1997).

The concept of a novel VRET exercise program, as a possible treatment for pain catastrophization toward exercise therapy in patients with FMS, may provide physiotherapists with a possible tool to address the psychological issues as well as the physical issues in the management of FMS. By incorporating a VRET program into physiotherapy practices, physiotherapists will not only be involved in prescribing exercise therapy in the management of FMS, but could also become involved in changing existing negative thoughts (catastrophizing thoughts) that the patient may have about exercises, possibly increasing compliance towards exercise programs. Fundamentally, by reducing pain catastrophization towards exercise activities in patients with FMS, fear-avoidance behaviours could be reduced and compliance towards prescribed exercise programs could be increased. The real benefits of exercise in FMS could therefore be realized by more patients and health providers.

CHAPTER TWO

FIBROMYALGIA SYNDROME

"Rebel without a cause"

2.1 Introduction

The complexities and ambiguities surrounding Fibromyalgia syndrome (FMS) have intrigued researchers across the globe for centuries (Peterson et al., 2007). Subsequently, an extensive body of literature for FMS currently exists from which a variety of theoretical perspectives can systematically be derived. However, the novelty of the concepts underpinning the research reported in this thesis warranted a slightly different approach to simply conducting a conventional systematic review of the available literature. Theoretical perspectives had to be derived from a wider, albeit still focused, understanding of the current evidence.

The following chapter therefore presents a targeted review of the current literature into FMS, specifically focusing on the research topics which logically contributed to the derivation of the theoretical perspectives which underpin the conceptualization of the research presented in this thesis. The targeted review follows a structured and logical interpretation of the literature using a *realist* synthesis framework as described by Pawson *et al.* in 2005. Unlike a conventional systematic review, a realist review provides a "*richer, more detailed and highly practical*" understanding of a concept (Pawson et al., 2005, pg.S1:21), which was likely to be of more pertinence to the particular research presented in this thesis. A brief description of how the realist review presented in this chapter was conducted is provided.

2.2 Methods

According to Pawson *et al.* (2005), a targeted realist review employs a similar, yet less stringent, methodology than a systematic review to retrieve the best evidence available to justify and support the theoretical perspectives which underpin the conceptualization of the research presented in this thesis.

2.2.1 Purpose of review

The purpose of this realist review was to explore the current available evidence into a number of key theories which would allow the derivation of the theoretical perspectives which underpin the conceptualization of the research presented in this thesis.

The key theories explored were as follows:

- The current definitions of FMS
- Controversies surrounding the existence of FMS
- The rising publication rates of FMS research
- FMS symptoms and characteristics
- The aetiology of FMS
- Current management of FMS
- Current challenges in the successful implementation of exercise therapy as a FMS management strategy in practice
- Current evidence into the management of pain catastrophization in FMS
- Cognitive-behavioural therapy (CBT) as treatment for pain catastrophization in FMS
- Advances in the measurement of chronic pain outcomes

2.2.2 Literature search and selection

The following main electronic bibliographic databases accessible through the Stellenbosch University's Medical Library were searched: *MEDLINE, Cochrane Library* and *BIOMED*

Central. The main search terms were broad-ranging and included medical subject headings (MeSH) and text terms, such as *fibromyalgia, fibromyalgia syndrome, chronic pain, exercise, exercise therapy, compliance, adherence, non-compliance, non-adherence, pain catastrophization, pain catastrophizing, catastrophization, fear-avoidance behaviours, kinesiophobia, pain-related fear; virtual reality exposure therapy, functional magnetic resonance imaging/fMRI, imaging, aetiology/etiology,* and *prevalence.* No date limits were applied to any of the databases and all publications were considered, irrespective of the publication language, country or type. However, in an attempt to minimize selection bias of articles and to ensure high-quality evidence was selected, meta-analyses or systematic reviews reporting on the specific topics covered in this targeted review were preferential and were sought where possible. If no meta-analysis or systematic review could be found, other types of publications such as traditional literature reviews or overviews, randomized controlled trials, non-randomized trials, cohort studies, case-control studies, case series studies, etiologic/epidemiologic studies, as well as editorials/letters to the editor, were retrieved and included in this review. Where possible, the English versions of non-English publications were obtained from the authors.

2.2.3 Data extraction and analysis

Since a realist review methodology was followed for this chapter and not the conventional systematic review methodology, the extraction and analysis of the data was handled a little differently. On selecting studies which met the broad criteria stipulated in 2.2.2, and which were deemed appropriate by the principal researcher to be included in the review; the studies were retrieved and filed according to the key theories they best represented.

2.3 The Literature

The following section presents a discussion of the literature selected following the literature search:

2.3.1 The current definitions of FMS

FMS is currently defined as a non-inflammatory, non-articular chronic rheumatologic disorder, primarily characterized by persistent widespread pain, stiffness, allodynia, hypersensitivity to painful stimuli, chronic fatigue, dyscognition and functional disability (Turk et al., 2004, Clauw et al., 2009; Clauw et al., 2011). However, since a clear and concise aetiology for FMS currently does not exist (Peterson et al., 2007; Buskila et al., 2009), and the definition is generally formulated using the widespread characteristics of FMS; other common definitions reported in the literature include, but are not confined to the following:

- "*Fibromyalgia is the diagnosis given to individuals with chronic widespread musculoskeletal pain for which no alternative cause, such as tissue inflammation or damage, can be identified*" (Clauw et al., 2009).
- "*Fibromyalgia is a condition marked by chronic widespread pain and multiple symptoms, including fatigue, sleep disturbances, cognitive dysfunction, and depressive episodes*" (Bennett et al., 2007).
- "*Fibromyalgia is now believed to be, at least in part, a disorder of central pain processing that produces heightened responses to painful stimuli (hyperalgesia) and painful responses to non-painful stimuli (allodynia)*" (Clauw et al., 2009).
- Fibromyalgia should be thought of as a "*metaphor or construct rather than a discrete diagnosis that best applies to some individuals with prominent central nervous system contributions to their chronic pain*" (Ablin et al., 2010).

Of concern is that an unclear definition of FMS limits comparisons of FMS populations globally. However, as technology and research advances, and the ambiguities surrounding

FMS are unveiled, it is anticipated that the definition of FMS may become more accurate over time.

2.3.2 "What have we created?": Controversies surrounding the existence of FMS

Controversially, however, Hazemeijer *et al.* (2003) proposes the following definition for FMS, negating the existence of FMS and epitomizing the complexity of FMS: "*Fibromyalgia is not an entity that can be described and explained; it is rather a subjective experience comprising pain and fatigue: a puzzling syndrome*." Despite the development of diagnostic criteria for FMS by the American College of Rheumatology (ACR) (Wolfe et al., 1990; Wolfe et al., 2010), and the acceptance of the diagnosis of FMS by prominent international health organizations such as the World Health Organization (WHO) (Baldry., 2001); the disorder still causes considerable debate between various healthcare professionals and disciplines (Govender et al., 2009). Arguments are mainly centered around the actual existence of the disorder and the validity of labeling FMS (Wallace et al., 2001; Hazemeijer et al., 2003) versus the taxonomy and probable causes of FMS (Govender et al., 2009).

Arguments relating to the actual existence of FMS are based on the postulation that FMS was, in fact, created by the therapeutic domain and that the manifestation of FMS symptoms is driven by the labeling of the disorder (Hazemeijer et al., 2003). According to Hazemeijer *et al*. (2003), doctors as well as the media have to change the therapeutic domain in order to prevent and treat FMS and that "*in such a renewed setting, fibromyalgia cannot become manifest in an individual and thus fibromyalgia syndrome can no longer exist*." Hazemeijer *et al*. (2003) further strengthens their argument by stating that since FMS cannot objectively be demonstrated, it cannot truly exist.

Despite the fact that the debate as to whether FMS should be considered a discrete disorder and a legitimate condition or whether it merely represents a collection of symptoms common to a number of subjective complaints is ongoing; FMS is still being diagnosed at an alarming

rate in public and private sectors across the globe (Hazemeijer et al., 2003). Globally, the prevalence rates of FMS range from 0.5% to 5% (Sarzi-Puttini et al., 2008, Assumpção et al., 2009), with patients with FMS incurring significant costs to healthcare and industries annually (Caballero-Uribe et al., 2004; Sarzi-Puttini et al., 2008). FMS is therefore a costly disease and represents an economic problem for healthcare systems globally (Caballero-Uribe et al., 2004). Furthermore, due to the fact that the work capacity of an individual suffering from FMS is compromised, FMS has an impact on productivity, which has economic implications for a country (Assumpção et al., 2009). Since FMS has been defined using specific criteria by the ACR in 1990, work disabilities have grown by up to 25.3% in developed countries (Wolfe et al., 1990; Caballero-Uribe et al., 2004). In these countries, the direct health costs are considerable, and the indirect costs, arising from employment absenteeism and disability pensions, are double that of the general working populations (Sicras-Mainar et al., 2009). Total annual expenses for a patient with FMS entail more than twice the expenses incurred for a patient with ankylosing spondylitis and are similar to those with chronic low back pain (Sicras-Mainar et al., 2009). Although few prevalence studies and cost studies have been undertaken in developing countries, the extent of the economic burden of FMS in developed countries can be extrapolated to poorer countries, and the influence of FMS on the already stringent health budgets in developing countries can be anticipated.

Wolfe *et al.* (2010) therefore counteracts the argument posited by Hazemeijer *et al.* (2003) by stating that "*fibromyalgia will always exist regardless of the name given to the syndrome*". The counter-arguments are based on the fact that clinicians have an obligation towards a patient and that although FMS cannot be objectively demonstrated, the condition continues to have a "visible appearance" (Wolfe et al., 2010). Ultimately it is the patient who needs to be considered and not the therapeutic domains, or beliefs of clinicians (Wolfe et al., 2010).

2.3.3 The rising publication rates of FMS research

Despite the controversial opinions regarding the legitimate existence of FMS described in 2.3.2, one has to wonder why a condition like FMS, which is presumed to be "*all in the patient's head*" and to have been created by the therapeutic domain (Hazemeijer et al., 2003); continues to receive a phenomenal amount of attention in research. Figure 2.1 depicts the publication rate of FMS research over the past 66 years (1946 to mid-2012) (*information sourced from MEDLINE*). During this time period, a total of 6889 publications were indexed in MEDLINE alone, of which around 299 are meta-analyses or systematic reviews. It is therefore clear from this illustration, that researchers remain intrigued by FMS and are constantly looking to find clarity regarding this condition. In addition, with advances in medicine and technology, and the specific application of more objective outcome measurement tools such as functional magnetic resonance imaging (fMRI) which have provided new insights into chronic pain (Gracely et al., 2011); it can be expected that publication rates will only escalate over the next couple of years.

Notably, of the 6889 publications indexed in MEDLINE a mere 15 studies were conducted in Africa, of which nine were conducted in South Africa. The recent postulation that chronic conditions may in fact place a larger burden on already compromised healthcare budgets in poorer, developing nations (Walker et al., 2006; Derman et al., 2011; Igumbor et al., 2011), warrants further research into the prevalence and impact of FMS in developing countries.

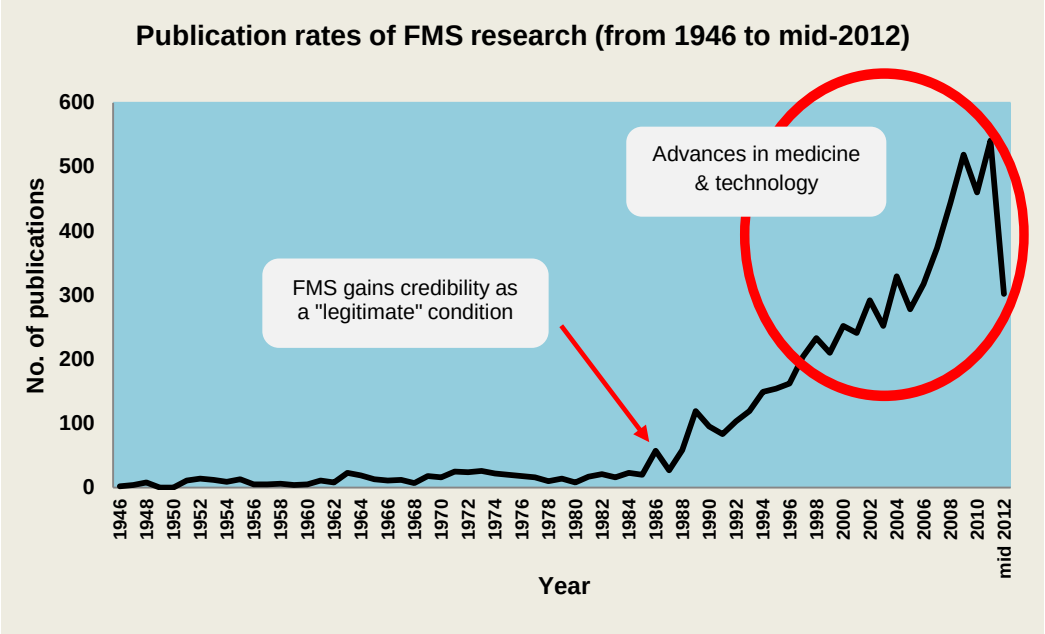


Figure 2.1: Publication rates of FMS research over the past 66 years (1946 to mid-2012)

2.3.4 The "Face" of FMS: symptoms and characteristics of FMS

One of the most perplexing characteristics of FMS is that the manifestation and severity of symptoms varies significantly between patients, and from day to day in the same patient. Although the primary criteria as suggested by the ACR for a positive FMS diagnosis is persistent widespread pain and hypersensitivity on palpation on at least 11 of the 18 tender points (Wolfe et al., 1990; Wolfe et al., 2010), FMS typically manifests in an array of combinations of the following symptoms (Peterson et al., 2007; Vincent et al., 2011):

- Chronic fatigue
- Allodynia
- Muscle stiffness
- Joint Stiffness
- Dyscognition (i.e. memory loss, disorientation, etc.)
- Functional disability
- Dysmenorrhea (painful menstrual periods)
- Chronic headaches
- Muscle twitches
- Weight gain
- Vision problems
- Urinary problems
- Depression
- Sleep disorders
- Dizziness
- Anxiety
- Nausea
- Skin problems
- Chest pain
- Multiple chemical sensitivity
- Sensitivity to bright light/loud noises

Although FMS can affect anyone, at any age; the prevalence of FMS is known to be much higher in women than men, and in middle-aged women (Tsang et al., 2008; Assumpção et al., 2009). It has been reported that FMS primarily affects more women than men by up to 1.67 times and that the male:female ratio for the prevalence of FMS is 1:9 (Bartels et al., 2009; Alabas et al., 2012). Reasons for this greater risk in females are however not yet well known, but various theories have been postulated (Lund et al., 2008; Bartels et al., 2009; Alabas et al., 2012). It may be possible that interacting factors including genetic, hormonal, biological, environmental, sociocultural, psychological and behavioural elements may cause FMS to develop more in females than males (Lund et al., 2008). Furthermore, the prevalence of FMS was estimated to be around 1.6% from age 30 to 39 years, and increased to 4.9% from age 40 to 49 years. However, the prevalence of FMS decreased to 3.7% from age 50 years onwards (Carmona et al., 2001; Häuser et al., 2011).

Albeit FMS may not be a life-threatening disorder, the symptoms of FMS can be prolonged and debilitating (Wallace et al., 2001). FMS negatively influences physical capability, intellectual activity, work capacity, emotional condition, personal relationships, professional career, and mental health (Sicras-Mainar et al., 2009), gradually reducing overall quality of life (Wallace et al., 2001).

2.3.5 "Rebel without a cause": The aetiology of FMS

Despite advances in medicine, the exact aetiology and pathophysiology of FMS are still not clearly understood (Peterson et al., 2007; Clauw et al., 2009; Buskila et al., 2009; Clauw et al., 2011). Over the years, a number of theories have been proposed to try and understand FMS (Peterson et al., 2007; Clauw et al. 2009; Buskila et al., 2009). The proposed causes for FMS include abnormalities in the neuroendocrine systems such as the hypothalamic-pituitary-adrenal axis, alterations in substance P levels and low-levels of cortisol, growth hormones, norepinephrine and serotonin (Peterson et al., 2007; Clauw et al., 2009).

The following section provides a basic overview of the current theories suggested in the development of FMS:

- *Hypothalamic-pituitary-adrenal axis dysfunction:* It is postulated that this hypothalamic-pituitary-adrenal axis dysfunction in patients with FMS may result in disturbances in the stress/adaption response which may result in elevated basal values of adrenocorticotrophic hormone and follicle-stimulating hormone, and decreased levels of insulin-like growth factor 1 and growth hormone (Tsigos et al., 2002; Mease., 2005). Several neurohormones may therefore play an important role in pain perception and may therefore be relevant in explaining FMS pain (Mease 2005; Peterson et al., 2007).
- *Low serotonin levels:* In patients with FMS, low serotonin levels are thought to result in depression, anxiety, pain, sleep disturbances and impaired smooth muscle function (Peterson et al., 2007; Buskila et al., 2009).
- *Elevated substance P:* A consistently high level of cerebrospinal fluid substance *P* has been found in patients with FMS (Russel., 2002; Patkar et al., 2003). Since increased levels of substance *P* are known to increase the sensitivity of nerves to pain and heighten awareness of pain, it is thought that when serotonin is low and substance *P* is high, an individual may experience more pain, possibly explaining the high levels of pain experienced by most patients with FMS (Russell., 2002; Patkar et al., 2003; Peterson et al., 2005).
- *Sleep disturbances:* Deep, restorative sleep is critical to the function of the nervous system and recuperation of the body's neuro-chemical processes. It is however postulated that in patients with FMS, deep and ''restorative'' sleep is repeatedly and excessively disturbed by rapid eye movement (REM) sleep. Anxiety, pain and drug usage seems to interfere with restorative sleep and hence appear to be the cause of FMS or worsen the condition (Peterson et al., 2007).

- *Stress responses:* Physiological responses triggered by stressful events can both protect and damage the body and have proven to be integral in the pathogenesis of a number of disorders (McEwen., 1998). During a stressful situation, the body aims to maintain a dynamic equilibrium in order to prevent a disturbance of adequate functioning. However, this homeostasis is often challenged by intrinsic or extrinsic stressors (Tsigos et al., 2002; Clauw et al., 2009). The body normally adapts to various stressors, by activating systems that assist in achieving homeostasis (McEwen., 1998). This reaction is commonly referred to as the "flight or fight" response. Prolonged activation of this response however results in adrenal hypocortisolism (altered release of cortisol or low levels of cortisol) which has been identified in FMS, post-traumatic stress disorder (PTSD), chronic fatigue syndrome, chronic pelvic pain and asthma, as well as in healthy people who have lived under ongoing stress (Heim et al., 2000). This mechanism, related to stress, may explain the development of FMS in certain individuals (Clauw et al., 2009).
- *Genetics:* Limited evidence exists to suggest that there may be a hereditary predisposition to developing FMS (Buskila et al., 2009). Several studies indicate a higher than normal occurrence of FMS in family members of patients with FMS and that these family members are also found to experience a high frequency of the symptoms related to FMS, i.e. irritable bowel syndrome and headaches (Clauw et al., 2011). Further research is however warranted to support this theory.
- *Pain perception:* As previously mentioned, the level of serotonin in FMS has been shown to be lower than in control subjects, while the concentration of substance *P* was found to be high in patients with FMS (Peterson et al., 2007; Clauw et al., 2009). In addition, Ang *et al.* (1999) observed that patients with FMS have a lowered pain threshold. It is therefore postulated that patients with FMS may perceive pain differently and abnormally (Clauw et al., 2009) which may contribute to the development of the condition.

2.3.6 Current management of FMS

Failure to identify a specific causal mechanism for FMS has resulted in a focus shift of the majority of research from aetiology to symptom management (Peterson et al., 2007; Sarzi-Puttini et al., 2008; Clauw et al., 2009; de Miquel et al., 2010). The management of FMS is therefore often adjusted to fit the patient's tolerance and symptom profile and requires careful management, continual re-evaluation of symptoms and appropriate adjustment of treatment (Sarzi-Puttini et al., 2008; Garcia-Campayo et al., 2008; de Miquel et al., 2010). Consequently, the primary goals of management in FMS are to control pain and increase function (Peterson et al., 2007; Sarzi-Puttini et al., 2008; Garcia-Campayo et al., 2008). Frustration around the management of FMS is that there is not a singular treatment modality that has been empirically proven to relieve symptoms in all patients (Sarzi-Puttini et al., 2008; de Miquel et al., 2010). Since FMS is symptomatically heterogeneous, the use of varying combinations of pharmacological (i.e. medications) and non-pharmacological interventions (i.e. exercise therapy, psychological treatments and physical modalities) for FMS symptoms is therefore recommended (Sarzi-Puttini et al., 2008; Boomershine et al., 2009; de Miquel et al., 2010).

The following section provides a brief overview of the treatments commonly incorporated into the management of FMS:

2.3.6.1 Pharmacological interventions

Pharmacological therapies such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), opioids, non-steroidal anti-inflammatory drugs (NSAIDs), growth hormone, corticosteroids and sedative hypnotics are typically used in the management of FMS (Häuser et al., 2012). The main objective for prescribing pharmacological agents in FMS is to improve sleep patterns, increase energy levels and reduce pain symptoms (Goldenberg et al., 2002; Boomershine et al., 2009), although there is currently no drug

which is capable of controlling overall symptoms in FMS (Di Franco et al., 2010). Physicians therefore often decide on single or combinations of drug therapies; and dosages are often altered, as well as types of medication, to best suit the patient's individual needs and the progression of the disorder (Di Franco et al., 2010).

One of the most widely-prescribed drugs in public and private sector for FMS is amitriptyline, a TCA (Fontenele et al., 2009; Smith et al., 2011). The widespread prescription of drugs such as amitriptyline is largely based on the fact that since sleep disturbances are thought to lead to the maintenance of FMS, improvement in sleep is required to improve overall FMS symptoms (Drewes., 1999; Smith et al., 2011; Häuser et al., 2012). Results from a recent meta-analysis indicate that TCAs such as amitriptyline have a significant effect on pain, sleep, fatigue and health-related quality of life with 48.3% of the patients in the amitriptyline treatment arm reporting a 30% pain reduction (NNT 4.9; 95% CI 3.5 to 8.0) compared to only 27.8% of the patients in the placebo treatment arm (Häuser et al., 2012). Physicians, as well as patients, should be aware of the potential benefits and adverse effects of using antidepressants (such as amitriptyline) in FMS (Nishishinya et al., 2008; Fontenele et al., 2009; Smith et al., 2011; Häuser et al., 2012). Although a small number of patients may experience a considerable amount of symptomatic relief when using amitriptyline, with no or minor adverse effects; the majority of patients stop their medication on their own accord because of the adverse effects they experience (Fontenele et al., 2009; Häuser et al., 2012). The results of a very recent meta-analyses that investigated the role anti-depressants have in FMS, found that the response rate (RR) of dropouts due to adverse events was 0.84 (95% CI 0.46 to 1.52; $I^2 = 0\%$) (Häuser et al., 2012).

Other antidepressants indicated in the management of FMS include nortriptyline, citalopram, fluoxetine, paroxetine, cyclobenzaprine, pregabalin, gabapentin, milnacipran, and duloxetine (Smith et al., 2011). In 2011, Smith *et al.* released a drug class review for the US

government regarding the pharmaceutical management of FMS. In this review it was reported that there is "*low-strength evidence that the short-term treatment with immediate-release paroxetine is superior to amitriptyline in reducing pain and sleep disturbances and provided low-strength evidence that there are no significant differences between amitriptyline as compared with cyclobenzaprine and nortriptyline"* among patients with FMS. The results of the review also indicated that although there were some significant differences between drugs in overall adverse events, they did not produce any differences in withdrawals due to adverse events among patients with FMS. The review also found low-strength evidence that duloxetine was superior to milnacipran on outcomes of pain, sleep disturbance, depressed mood, and health-related quality of life; and low-strength evidence that both duloxetine and milnacipran were superior to pregabalin on improvement in depressed mood, whereas pregabalin was superior to milnacipran on improvement in sleep disturbance among patients with FMS (Smith et al., 2011). The effect of amitriptyline was found to be similar to duloxetine, milnacipran, and pregabalin on outcomes of pain and fatigue among patients with FMS (Smith et al., 2011). Furthermore, although there were significant differences between duloxetine, milnacipran, and pregabalin in specific adverse events, these drugs did not produce any differences in overall withdrawals, overall adverse events, and withdrawals due to adverse events among patients with FMS (Smith et al., 2011). For the remaining drugs, the review found that there was only evidence of significant improvements in pain over placebo in one trial for gabapentin, in one of three trials for cyclobenzaprine, and in one trial of fluoxetine among patients with FMS (Smith et al., 2011). However, it was also found that duloxetine was not effective for pain reduction in male, non-white, and older patients based on a small sample size that was underpowered to detect a difference. Compared with placebo, duloxetine, fluoxetine, controlled-release paroxetine, and pregabalin, significantly improved FMS symptoms regardless of baseline depression but milnacipran was only effective in non-depressed patients (Smith et al., 2011). Controlled-release paroxetine and pregabalin was found to significantly improve FMS symptoms regardless of baseline anxiety

(Smith et al., 2011). No conclusions could however be made about comparative effectiveness or harms among these drugs since the numbers of trials/patients in placebo-controlled trials were too few to provide meaningful results in indirect comparisons (Fontenele et al., 2009; Smith et al., 2011).

2.3.6.2 Psychological interventions

Psychological interventions commonly employed in the management of FMS include CBT education, relaxation/biofeedback, behavioural treatment and mindfulness-based treatment. The constructs typically tackled in FMS using CBT include symptom reduction, coping strategies, and maladaptive illness behaviour (Glombieski et al., 2010). Education in the management of FMS primarily concentrates on providing the patient with reliable information about FMS. Although controversies still surround the disorder, information on possible symptoms, available treatments and stress management can still be provided. Education aims to empower the patient about their condition, allowing patients to take responsibility for their own healthcare. Although changes in pain beliefs and improved cognitive coping strategies have been found to be strongly correlated with both physical and psychological functioning (Glombieski et al., 2010); the results of a recent meta-analyses into the effects of psychological treatments in FMS, suggested that the effects of psychological treatments for FMS are relatively small and that CBT was associated with the greatest effect sizes (Glombieski et al., 2010). In another recent meta-analyses reporting on the effect of CBT in FMS, it was concluded that CBT may improve coping with pain to reduce depressed moods and healthcare-seeking behaviour in FMS, and should be considered in the management of FMS (Bernardy et al., 2010).

2.3.6.3 Physical and other treatment modalities

Although a host of physical modality treatments for FMS currently exist, the evidence available for the effect of each varies. To provide an idea of the current available evidence

for various physical modalities used in the management of FMS, an attempt was made to summarize the information by denoting the level of evidence for each modality. Since grading of evidence was not a main objective of this review, the results have to be viewed with caution since a conventional systematic review methodology was not followed. The National Health Medical Research Council (NHMRC) (Australia) hierarchy of evidence (table 2.1) was used to demarcate the current evidence available for a variety of physical and other treatment modalities for FMS.

Table 2.1: NHMRC hierarchy of evidence (NHMRC 2005)

Level of evidence	Study design
1	Evidence obtained from a systematic review of all relevant randomised controlled trials.
2	Evidence obtained from at least one properly-designed randomised controlled trial.
3-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
3-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
3-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
4	Evidence obtained from case series (post-test or pre-test/post-test).

In table 2.2, the current evidence available for the most common physical modalities used in the management of FMS is summarized:

Table 2.2: Evidence for the effect of physical and other treatment modalities in FMS

Modality	Level of evidence	Evidence source	Summary recommendation
Thermal therapy (heat therapy)	Level 2	> 1 RCT	Combined with sauna therapy and underwater exercise improved the QOL, pain and symptoms of patients with FMS (Matsumoto et al., 2011)
TENS	Level 2	1 RCT	Used in combination with other therapies, may be effective (Mutlu et al., 2012)
Ultrasound	Level 2	1 RCT	Used in combination with other therapies, may be effective for FMS (Çitak-Karakaya et al., 2006)
Biofeedback	Level 1	MA	May be beneficial for FMS; requires further study (Kayiran et al., 2010; Terhorst et al., 2011)
Massage	Level 1	MA	May be beneficial for FMS, inconclusive evidence (Terhorst et al., 2011)
Meditation	Level 1	MA	Improvement in FMS-related symptoms observed (Kalichman et al., 2010)
Acupuncture	Level 1	MA	Cannot be recommended as a single treatment option (Langhorst et al., 2010; Terhorst et al., 2011; Terry et al., 2012)
Balneotherapy (Spa therapy)	Level 1	MA	Effective intervention for FMS (Terhorst et al., 2011)
Spinal manipulation	Level 1	MA	Showed no benefit for use in the management of FMS (Terhorst et al., 2011)
Homeopathy	Level 1	MA	May be beneficial for FMS; inconclusive evidence (Perry et al., 2009; Terhorst et al., 2011., Terry et al., 2012)
Laser	Level 1	> 1 RCT	Used in combination with other therapies, may be effective for FMS (Gür et al., 2002; Fernández-Garcia et al., 2011; Panton et al., 2012)
Hydrotherapy	Level 1	MA	Moderate evidence for short-term effect on FMS symptoms (Langhorst et al., 2009)

Key: SR = systematic review; MA - meta-analysis; RCTs = randomized controlled trials; TENS = transcutaneous electrical nerve stimulation; CTM = connective tissue massage; MLDT = manual lymph drainage therapy; FMS=Fibromyalgia syndrome; QoL = Quality of Life

2.3.6.4 Exercise therapy

Exercise therapy is arguably one of the most common and most important modalities that physiotherapists across the globe use in practice, as both preventative and treatment strategies for a wide variety of musculoskeletal, neurological, cardio-respiratory, and sport-related conditions (Kelley et al., 2010; Kelley et al., 2011). A fundamental component of healthcare, the immediate and long-term physiological effects of exercise on the musculoskeletal, cardiovascular and respiratory systems are well-documented in the literature (Brosseau et al., 2008; Kelley et al., 2010; Thomas et al., 2010; Kelley et al., 2011).

Exercise therapy, particularly aerobic exercise, has consistently been shown to be one of the most efficacious management strategies for FMS (Williams et al., 2009). In a well-conducted trial involving 20 weeks of cardiovascular fitness training, 18 patients with FMS demonstrated clinically and statistically significant improvements in overall symptoms (Williams et al., 2009). It has also been reported that aerobic training significantly improved: 1) aerobic performance in patients with FMS by up to 17.1% in the exercise group versus 0.5% in the control group, 2) tender point pain pressure threshold by up to 28.1% decrease in the exercise group versus 7% decrease in the control group and 3) pain by up to 11.4% decrease in the exercise group versus 1.6% in the control group (Kelley et al., 2010; Kelley et al., 2011). Furthermore, the improvements in FMS symptoms due to the aerobic exercise were sustained over a period of time (Williams et al., 2009). Recent clinical guidelines therefore recommend exercise therapy as a key component in the management of FMS (Brosseau et al., 2008; Busch et al., 2011).

2.3.7 Current challenges in the successful implementation of exercise therapy in FMS practice

Though most health professionals are aware of the benefits of exercise for FMS; many express frustrations with the fact that patients' compliance is particularly poor with the recommended exercise programs (Jones et al., 2009). Non-adherence to prescribed exercise programs in FMS in particular, can however possibly lead to weakening of the musculoskeletal system, functional disability and more pain (Jones et al., 2009). The most common reasons for patients with FMS not adhering to the prescribed exercise programs is that they 'over-predict' the amount of pain a particular activity may give them, or that they fear that their symptoms may 'flare up' (Jones et al., 2009). This belief that the 'worst possible outcome will occur' is commonly referred to as pain catastrophizing (Hassett et al., 2000), a cognitive strategy broadly defined as '*an exaggerated negative orientation towards actual or anticipated pain experiences"* (Sullivan et al., 1995).

Over recent years, pain catastrophization has shown associations with functional disability, pain severity, elevated disease activity and depression in chronic pain patients (Quartana et al., 2009; Engel-Yeger et al., 2011). Assumed to be more pronounced in patients with FMS than in any other chronic pain patient population; pain catastrophization often leads to the development of fear-avoidance behaviours and non-adherence towards prescribed exercise programs among patients with FMS (Edwards et al., 2006; Hassett et al., 2009; Jones et al., 2009). Since inactivity among patients with FMS is particularly detrimental and typically results in the deconditioning of the musculoskeletal system and increased FMS symptoms; the presence of pain catastrophization poses various challenges to the effective management and maintenance of physical function among patients with FMS (Hassett et al., 2009). Pain catastrophization is thus currently recognized as a barrier to the healthy re-establishment of psychological and physical functioning among patients with FMS (Quartana et al., 2009).

The role of pain catastrophization and the subsequent development of fear-avoidance behaviours in chronic pain conditions have been well reported in the literature. In 2000, Vlaeyen and Linton proposed a cognitive behavioural model to explain the association between chronic pain, pain catastrophizing, fear of pain and disability (Leeuw et al., 2007). This particular model, namely the *Fear-avoidance model of Chronic pain* (see figure 2.2), suggests that the way in which pain is interpreted leads to different behavioural pathways (Leeuw et al., 2007). Dysfunctional interpretation of pain particularly gives rise to pain catastrophizing thoughts which in turn gives rise to fear-avoidance behaviours (a specific fear of a movement or task, based on the belief that it will result in (re)injury) (de Gier et al., 2003; Leeuw et al., 2007). According to Leeuw *et al.* (2007), the fear-avoidance model, pain catastrophizing and fear-avoidance behaviours are interlinked in the way that a catastrophizing response to pain initiates fear of movement/(re)injury which leads to fear-avoidance behaviours.

FEAR-AVOIDANCE MODEL OF CHRONIC PAIN

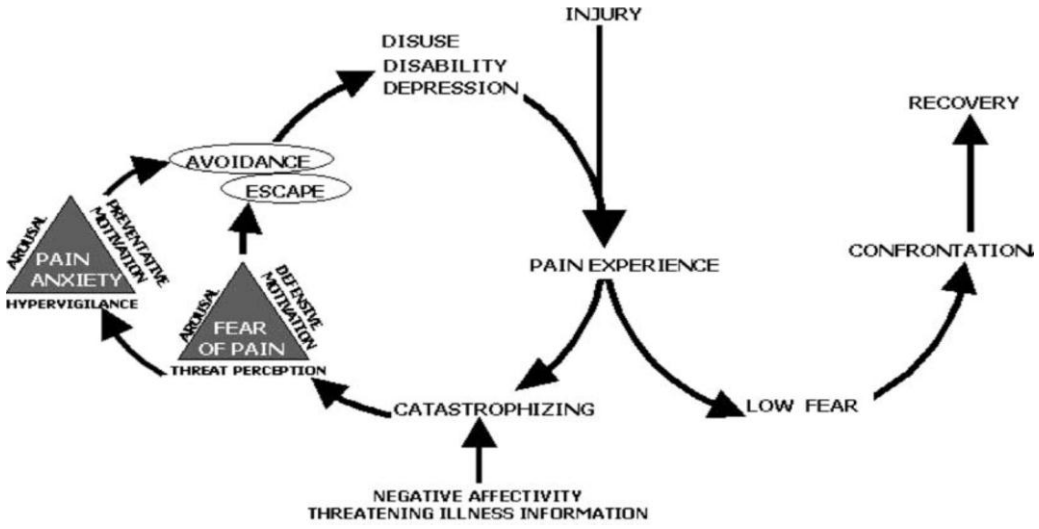


Figure 2.2: Fear-avoidance model of Chronic Pain (Reproduced with permission: Leeuw et al., 2007)

In chronic pain however, avoiding the pain is not possible; the patient simply avoids the perceived threat (Leeuw et al., 2007). Among patients with FMS, the perceived threat is often exercise activities as patients fear that exercises will increase their pain and symptoms. FMS patients who therefore catastrophize exercise activities, will essentially develop a fear of movement/(re)-injury and avoid or do not adhere to prescribed exercise therapy programs. This is of concern since non-adherence to exercise therapy programs or the avoidance of physical activity altogether in chronic pain sufferers, leads to functional disability due to disuse (*see Fear-avoidance model)* (Leeuw et al., 2007). According to Leeuw et al., 2007), pain catastrophizing has a significant influence on pain perception, on the ability to predict pain chronicity and on the individual's response to pain treatment. Further, the recent presumption that pain catastrophizing influences the attentional focus on painful or potentially painful stimulus (results from an fMRI study), suggests that the threat of the stimulus may be an important mediator of altered pain perception (Gracely et al., 2004). Pain catastrophizing is therefore an important cognitive factor contributing to the maintenance of chronic pain in FMS sufferers and should be considered when treating FMS (Leeuw et al., 2007).

2.3.8 Current evidence into the management of pain catastrophization in FMS

Despite the proposed importance of pain catastrophization in the maintenance of chronic pain in FMS, there is a dearth of research into the treatment of pain catastrophizing in FMS. To our knowledge, only three studies currently exist regarding the treatment of pain catastrophizing in patients with FMS (Nelson et al., 2006; Rodero et al., 2008; Alda et al., 2011). The following section discusses the results of each of these studies.

The first study conducted by Nelson *et al*. in 2006 reports on the development and evaluation of a psychological treatment for pain catastrophizing in patients with FMS. This study incorporated a case study design and consisted of two parts. The first section of the

study consisted of a survey aimed at collecting data to develop an intervention (n=39). The second part of the study piloted the developed intervention (n=7). The developed intervention consisted of a psychoeducational (2 hour session) guided by written materials for patient and facilitator which included didactic information about catastrophization and its effects on adjustment to chronic pain, cognitive strategies to promote self-efficacy in pain management, and in-session practice and discussion of relaxation skills. Teaching strategies for social learning were also incorporated. The goals of the intervention were to identify ways of thinking about pain; to identify how this affects the way in which an individual functions physically and emotionally; to understand what catastrophizing means; and to identify ways in which to specifically change negative thinking about pain. The components of the developed intervention are depicted in Table 2.3. The findings of this study suggested that a brief, psychoeducational program which targets the reduction of pain catastrophizing in patients with FMS may be a feasible addition to the usual FMS treatment program (Nelson et al., 2006). However, further larger studies are warranted to confirm the findings of this study.

The second study piloted ‘imagined exposure therapy”, a new approach in CBT, on eight subjects using a quasi-experimental study design (Rodero et al., 2008). The study incorporated an available ten-session CBT program and added one extra session of imagined exposure therapy. Each session was between 30 and 60 minutes in duration. The 11 CBT sessions incorporated in the study are depicted in Figure 2.3. The results of the study suggested that the imagined exposure may be effective in decreasing rumination in patients with FMS who catastrophized (Rodero et al., 2008). Again, the results of this study should be viewed with caution since the study sample size was extremely small (n=8).

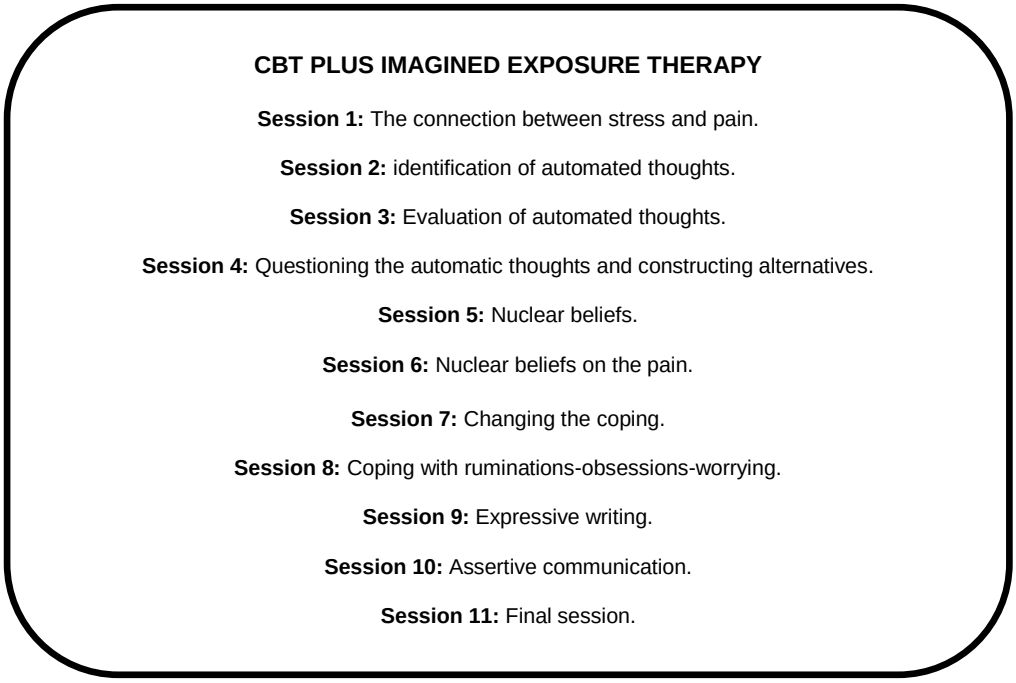


Figure 2.3: CBT sessions used by Rodero et al., 2008

The third study, a recent RCT, assessed the effectiveness of CBT and the recommended pharmacological treatment compared with treatment as usual at the primary care level for the treatment of pain catastrophization in patients with FMS (Alda et al., 2011). The study consisted of a six-month, multicenter, RCT in which patients were randomly assigned to one of three study arms: CBT (n = 57), recommended pharmacological treatment (n = 56) and treatment as usual at the primary care level (n = 56). The major outcome of this study was pain catastrophizing in patients with FMS. The CBT intervention mainly consisted of two major components: cognitive restructuring, which focused on reducing pain-specific dysfunctional cognitions (primarily pain catastrophizing), and coping, which focused on teaching cognitive and behavioural coping strategies. The intervention encompassed ten weekly 90-minute CBT group sessions, including nine standard CBT sessions and one specific session on pain catastrophizing (session eight) that were structured similarly to the program reported in Rodero *et al.* (2008), except it did not include a final (11^{th} session) (Figure 2.3).

The eighth session was directed especially at participants who showed high levels of rumination (a subsection of catastrophization) and consisted of instructing these individuals to write a story regarding the worst possible scenario for the future, based on their greatest fear. The story was audio recorded and patients were instructed to listen to this story for 30 to 60 minutes until it no longer caused anxiety. This process took between 10 and 15 sessions. The duration of the intervention was ten to 12 weeks. The study results indicated that “CBT” showed a higher efficacy than the recommended pharmacological treatment and treatment as usual, not only in key outcomes in FM, such as function and quality of life, but also in relevant mediators of treatment effects, such as pain catastrophizing and pain acceptance (Alda et al., 2011).

TABLE 3. Components of the Program

Content/Goal	Minutes in Session	Activities to be Used	Theoretical Basis	Sources of Information (Bandura)
Introduction to purpose of session/Patient begins to identify personal goal	5 minutes	Didactic presentation	Self-efficacy theory Group therapy Adult learning principles	Facilitator as "expert" in pain management Verbal persuasion by facilitator of value of goal-setting and cognitive changes
Brief introduction of patients and family members/ Patient identifies commonality with others. Patient identifies relationship of thoughts about session/FM to feelings/pain.	10 minutes	Introductions	Self-efficacy theory Group therapy Adult learning principles	Vicarious learning from others in the group about relationship of thoughts and pain experience Physiologic arousal (↓ anxiety by identifying commonalties in the members)
Self-assessment of use of catastrophizing (patient)/response to catastrophizing (family member)/Patient increases awareness of thought patterns	10 minutes	Written exercise	Adult learning principles Stress management Self-efficacy theory	Performance accomplishment through recognition of catastrophizing thoughts and ability to monitor/change negative thinking
Ways of thinking about pain; cycle of thoughts, emotions, pain coping, and responses of others/Patient identifies relevant parts of pain cycle that interfere with functioning.	20 minutes	Didactic presentation	Self-efficacy theory Assertiveness theory	Verbal persuasion by investigator of importance/success of patient in changing thoughts Role-modeling by facilitator of effective communication skills
Wrap-up	5 minutes	Q & A session	Self-efficacy theory Group therapy	Verbal persuasion of patient's development of cognitive skills
Session break	10 minutes			Role-modeling by facilitator of need for pacing of activity, need for regular breaks for persons with chronic pain
Ways to change thinking and communication patterns/patient recognizes ways to interrupt pain/thought cycle (journaling, distraction, other self-care management strategies)	15 minutes	Role modeling Role playing Group discussion Written exercise	Self-efficacy theory	Step in performance accomplishment by practicing skills Vicarious learning of ways to change thinking Role-modeling by facilitator of importance of self-affirmation while learning new skills
Relaxation/patient experiences decreased tension and can verbalize a strategy to achieve relaxation.	30 minutes	Group discussion Group exercise using passive muscle relaxation	Stress management Self-efficacy	Physiologic arousal-decrease by recognition of muscle tension-pain relationship
Individual goal setting/use of journal and other resources/patient identifies a weekly goal and strategy to use to decrease catastrophizing. Review completion and mail return of homework assignments. Discuss weekly phone calls.	20 minutes	Group discussion Review of written homework for Week 1	Adult learning principles Self-efficacy theory	Step to performance accomplishment (mastery) by setting goals Role-modeling by facilitator of steps to use in goal-setting, plan of strategies to use to meet goals, rewarding self for achievements
Wrap-up	5 minutes	Termination of session	Group therapy	Verbal persuasion

Table 2.3: Components of the intervention developed by Nelson et al., 2006 (reproduced with permission)

2.3.9 CBT as treatment for pain catastrophization in FMS

Exposure therapy is a generally safe, CBT treatment which involves exposing the individual to a task or movement that he/she fears until the emotion of fear is alleviated and disassociated from that particular task or movement (Encyclopaedia of Mental Disorders). Experimental support for this concept is provided by the 'match/mismatch' model of pain (Rachman et al., 1992) which states that people initially over-predict how much pain they will experience, but after a few exposures these predictions tend to be corrected to match with the actual experience.

Traditionally, exposure therapy is conducted during real situations, namely in vivo exposure; or during an imagined situation, namely imagined exposure. As already mentioned in the previous section, imagined exposure has been previously piloted on eight patients with FMS with favourable results (Rodero et al., 2008). However, more recent innovations indicate that exposure therapy can be administered via virtual reality, namely virtual reality exposure therapy (VRET) (Encyclopaedia of Mental Disorders). VRET has been proposed as the new way of conducting exposure therapy because it can provide a sense of being in the feared situation, without actually being in the feared situation. This may prove useful for people who have difficulty imagining situations or concentrating, and for people who want a greater sense of control and can thus turn the "virtual situation" on and off at their command when things become too much to handle. To date, VRET has been used to treat panic disorders, social phobias, fear of flying, fear of spiders and fear of heights (Powers et al., 2008). No studies currently exist investigating the effect of VRET on pain catastrophizing in FMS.

2.3.10 Advances in the measurement of chronic pain outcomes

The establishment of more objective measurements for chronic pain was warranted to advance the understanding of pain mechanisms involved in the development and maintenance of chronic pain, and in doing so, improve the management of chronic pain.

As a result, over the past decade there has been a significant increase in the use of more objective measures to enhance the current understanding of chronic pain (Borsook et al., 2006). An objective and valid measure which has received considerable attention and has gained admirable respect for revolutionizing the current misunderstood concepts of chronic pain within the scientific circles is functional imaging (Borsook et al., 2006). With the use of fMRI, chronic pain has already been re-categorized as a degenerative disease (Borsook et al., 2006). fMRI has also slowly begun unveiling the remaining ambiguities and perplexities surrounding conditions such as FMS (Gracely et al 2004). It is now known that the presence of chronic pain may actually alter the central nervous system (CNS) (Borsook et al., 2005) and this has been evaluated and confirmed across a number of various diseases including FMS (Gracely et al., 2004); chronic back pain (Giesecke et al., 2004); and irritable bowel syndrome (Verne et al., 2003). The studies report that during functional imaging of FMS and chronic back pain, responses to thermal or mechanical stimuli that are applied hetero-topically (i.e., away from the actual location of the pain) are enhanced and are present in a number of CNS regions, including non-sensory regions of the brain (Borsook et al., 2006). Significantly greater frontal lobe activation in chronic pain sufferers has also been commonly observed (Apkarian et al., 2005). This finding suggests that in chronic pain patients, the activity of the CNS in regions involved in cognitive processing differs between acute and chronic pain. fMRI studies into chronic pain mechanisms have also found neuronal loss occurring in significant pain pathways such as in the thalamus and the lateral prefrontal cortex (Apkarian et al., 2004) of chronic pain patients when compared to controls although the exact role of this neuro-degeneration in producing either the altered CNS responses or the pain state is not yet fully understood (Borsook et al., 2006). Nevertheless, it has been postulated that maladaptative changes in non-sensory circuits may contribute to the psychological constructs such as depression, anxiety and amotivation that are often observed in the chronic pain patients (Borsook et al., 2006). The increased recognition that multiple neural systems may be involved in pain processing and affect pain perception

suggests that multiple neural systems are likely affected in chronic pain. From the results published thus far, it can be deduced that the assessment of pain intensity is probably not a good indicator for changes in chronic pain states and that functional imaging of the neural system may be able to better classify the correlation between activation in the CNS and self-reported responses of patients to subjective questionnaires (Borsook et al., 2006). In addition, the term “centralization of pain”, first proposed by McKenzie in the 1950’s, has evidently now become more accurate in describing the mechanisms underpinning chronic pain. It is therefore believed that the application of fMRI in chronic pain is the key to better understanding chronic pain mechanisms in a bid to help identify and develop new and more effective treatments (Tracey et al., 2001; Borsook et al., 2006).

Imaging in chronic pain is however, not without any limitation. A major concern is that in chronic pain it is usually difficult to recruit a homogenous group of subjects who display similar symptoms, duration of disease, etc. since chronic pain patients vary significantly in presentation and medical history. The inability to study a homogenous group of subjects typically limits the study, the study outcomes, generalization of results, as well as potential comparison of study results across various research centers. However, it is encouraging to know that as fMRI and other imaging technologies become more sophisticated and more accessible, the understanding and evaluation of chronic pain may advance swiftly and current limitations and logistical issues can be adequately addressed (Akparian et al., 2005; Borsook et al., 2006).

2.3.10.1 *Advances in the measurement of pain catastrophizing in FMS*

Traditionally, pain catastrophization has been subjectively measured using validated self-reported outcome measurement tools. One of the most common self-report outcome measures used to subjectively quantify pain catastrophization in clinical practice and research is the Pain Catastrophizing Scale (PCS). Initially developed in English by Sullivan

et al. in 1995; the original PCS is considered a 'broader, reliable and valid measure of catastrophization". The items integrated into the original scale were specifically intended to assess elements of pain catastrophization (Sullivan et al., 1995). The PCS is thus a useful tool to identify individuals who may be susceptible to amplified negative responses towards pain and the anticipation of pain. Numerous validation studies have since shown that the PCS has a concrete factor structure, credible psychometric properties (i.e. internal consistency, test-retest reliability and validity) and is correlated to other health outcomes such as pain intensity, pain-related disability, fear-avoidance behaviours and psychological distress (Monticone et al., 2011; Marić et al., 2011; Pallegama et al., 2009; Garcia-Campayo et al., 2008; Meyer et al., 2008; Miró et al., 2008; Yap et al., 2008; Tremblay et al., 2008; French et al., 2005; Sang-Cheol et al., 2004 and Crombez et al., 1999) .

Recently however, the neural correlates of pain catastrophizing in patients with FMS were examined using fMRI (Gracely et al., 2004). The study found that pain catastrophizing in patients with FMS was significantly associated with increased brain activity in areas related to anticipation of pain (contralateral medial frontal gyrus and ipsilateral cerebellum) and attention to pain (ACC and bilateral dorsolateral prefrontal cortex) as well as to emotional (ipsilateral claustrum, interconnected to the amygdala) and motor responses (contralateral lentiform nuclei) and were significantly associated with pain catastrophizing (Gracely et al., 2004). It was established that "*pain catastrophizing influences pain perception through altering attention and anticipation, and heightening emotional responses to pain"* (Gracely et al., 2004). Gracely *et al.* (2004) therefore concluded that the fMRI findings of their study provide "*valuable insight into the cognitive mechanisms which support and maintain"* pain catastrophizing which may assist in the improvement of treatment efficacy for FMS. Accordingly, it was recommended that management approaches for FMS which aimed to reduce the attention, anticipation and emotional responses to pain, and essentially modify behaviours in FMS, may result in better treatment outcomes (Gracely et al., 2004).

2.3.11 Bridging the gap...

Exercise therapy is an active treatment which requires the co-operation of the individual for optimum results to be achieved (Jones et al., 2009). However, most individuals are not dedicated enough to remain compliant to the exercise programs and will often opt for less active, although less effective, treatments such as medications (Cameron et al., 1996). It is thus important that prior to prescribing exercises to patients with FMS (a group who has been recognized for displaying high levels of non-compliance to treatments), physiotherapists adequately prepare and educate patients about the benefits of exercises and what they can expect during the program. Essentially, physiotherapists are in a prime position to change patients' negative thoughts about exercises. Since exercise therapy is consistently found to be an effective management strategy for FMS, the concern that cognitive factors such as pain catastrophizing may influence patient compliance to exercise therapy, justifies further research in this area (Hassett et al., 2000; Ablin et al., 2010; Gowans et al., 2010). In theory, it stands to reason that targeting pain catastrophization in patients with FMS may be the answer to improving adherence to exercise programs.

According to the 'match/mismatch' theory proposed by Rachman *et al*. in 1992, a few exposures to the painful stimulus can diminish or eliminate predictions of excessive pain in response to a painful stimulus. It may then be worthwhile investigating the effect of exposure therapy on pain catastrophizing in patients with FMS. Empirical evidence suggests that imagined exposure therapy, may be useful in the alteration of pain catastrophization observed in patients with FMS (Rodero et al., 2008). However, recent innovations indicate that exposure therapy may also be administered via virtual reality technology, namely *virtual reality exposure therapy (VRET)* or in virtuo exposure therapy (Parson et al., 2008; Powers et al., 2008). Contrary to imagined exposure therapy, VRET seems ideal for conditions where an individual finds it difficult to imagine various situations (Parson et al., 2008; Powers et al., 2008; Rodero et al., 2008). To date, VRET has successfully been used for a variety of

phobias, such as fear of spiders and flying, but has never been used in the treatment of fear of movement/exercise, nor for pain catastrophizing in chronic pain conditions.

Since there is no available VRET program for the treatment of pain catastrophizing in patients with FMS, preliminary steps were required prior to the development and testing of such a program. Initially, it had to be ascertained if visual exposures to catastrophized exercise activities cognitively triggered the functional brain areas associated with pain catastrophizing in patients with FMS. The premise was that if visual stimuli of the catastrophized exercise activities cognitively trigger pain catastrophizing in previously identified functional brain areas of patients with FMS (Gracely et al., 2004); a VRET program aimed at exposing patients with FMS to visuals of the feared or catastrophized exercises and neutralizing feelings of catastrophization towards exercise activities, could possibly decrease pain catastrophizing and subsequently decrease fear of movement. In turn, compliance towards prescribed exercise programs may be increased. The concept of developing a VRET exercise program as a treatment option for pain catastrophizing to improve compliance towards exercise programs in FMS therefore seems plausible (Rodero et al., 2008).

2.4 Chapter Summary

- The aetiology of FMS remains unknown.
- The global prevalence rates of FMS range from 0.5% to 5%.
- FMS primarily affects more women than men by up to 1.67 times.
- The typical FMS patient is a menopausal woman with a history of victimization
- FMS represents an economic problem for health care systems globally.
- FMS negatively affects the patient's quality of life.
- FMS management consists of a combination of pharmacological and non-pharmacological therapies.
- Exercise therapy is efficacious in the management of FMS symptoms.
- Implementation of exercise in the management of FMS is hampered by poor compliance.
- A key predictor of poor compliance in FMS is pain catastrophization.
- The role of pain catastrophizing is believed to be more pronounced in FMS.
- Dysfunctional interpretation of pain gives rise to pain catastrophizing which leads to fear-avoidance behaviours, which results in attrition of physical activity.
- Inactivity is detrimental in FMS.
- There is limited research into the management of pain catastrophizing in FMS
- Inference that pain catastrophization and subsequent fear-avoidance behaviours may influence the compliance of patients with FMS to exercise programs, justifies considering the alteration of pain catastrophizing in the management of FMS.
- CBT, specifically exposure therapy, may be useful in the alteration of pain catastrophization observed in patients with FMS.
- Imagined exposure therapy was found to be effective in decreasing pain catastrophization in patients with FMS.
- VRET has never been used in the treatment of fear of movement/exercise, nor pain catastrophizing in chronic pain conditions.
- fMRI has begun to unveil the ambiguities and perplexities surrounding FMS.
- Pain intensity is not a good indicator for changes in chronic pain states.
- Limited research into FMS available on South African populations.

2.5 Conceptualization of theoretical perspectives which underpin this research

Based on the literature reviewed in chapter two, a number of theoretical perspectives were derived which underpin the conceptualization of the research contained in this thesis. The novel concept, set out to be proven or negated in this research, was that a specially-designed VRET program may be a plausible option to consider as treatment for pain catastrophization in patients with FMS.

Figure 2.6 presents a flow diagram of how the theoretical perspectives derived in this chapter were addressed in the thesis chapters.

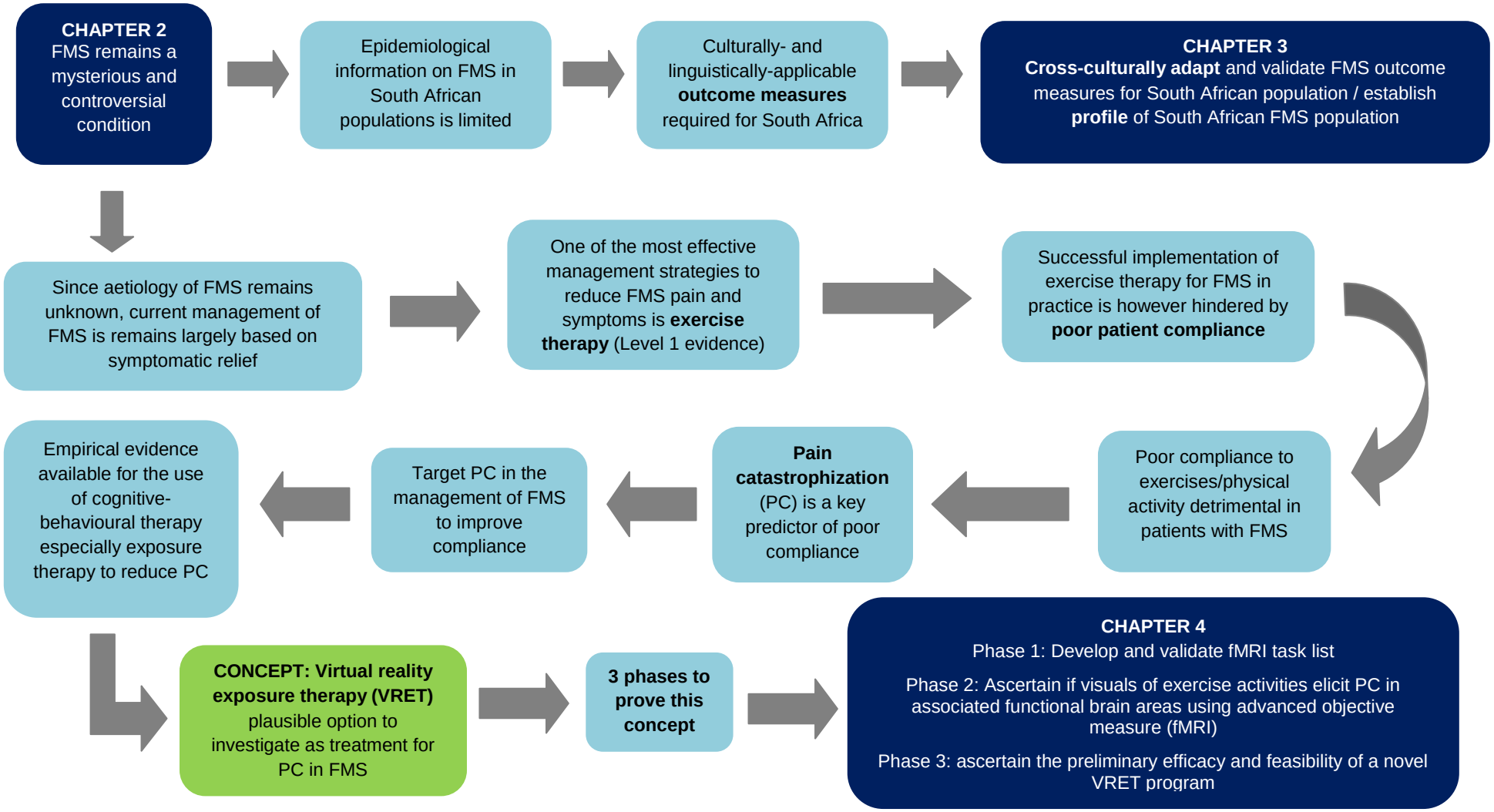


Figure 2.6: Flow diagram illustrating how theoretical perspectives were addressed in the thesis chapters

CHAPTER THREE

FIBROMYALGIA SYNDROME IN SOUTH AFRICA

Cross-cultural adaptation of various outcome measures and profile study among South African Fibromyalgia patients

3.1 Introduction

Across the globe, populations and cultural sub-groups within populations, typically differ in language, dialect, lifestyle, morals, values, behaviour, customs, beliefs, perceptions of life and expression of disease (Guillemin et al., 1993; Gonzalez-Calvo et al., 1997; Beaton et al., 2000). The direct administration of existing and previously validated versions of self-report outcome measures in various countries, cultures and language groups, is therefore not always possible or advised. In these instances, misinterpretations of the questions or scoring systems, and culturally-inappropriate anchors or references, may compromise the integrity and validity of the responses that the outcome measure seeks (Guillemin et al., 1993; Beaton et al., 2000; Cook et al., 2006; Le Gal., 2010). The ramifications of utilizing linguistically- or culturally-inappropriate health outcome measures across various populations and cultures are therefore far-reaching; not only in terms of decisions made on effective care, but also in terms of health policies which may be developed from the research findings. Accurate measurement across cultures is thus dependent on the linguistic and cultural adaptation and application of an outcome measure for a specific population (Beaton et al., 1998; Beaton et al., 2000; Cook et al., 2006; Le Gal., 2010).

In the current research, a variety of outcome measures were used. These outcome measures included the Pain Catastrophization Scale (PCS), Tampa Scale for Kinesiophobia

(TSK) and the revised Fibromyalgia Impact Questionnaire (FIQR). Although Afrikaans versions of the PCS and TSK are available from the MAPI institute (www.mapi-trust.org), these outcome measures have not been previously validated in a South African population. Furthermore, Xhosa versions of all these outcome measures currently do not exist and therefore needed to be developed. The purpose of the following study was thus to cross-culturally adapt and validate the South African PCS, TSK and FIQR (SA-PCS, SA-TSK and SA-FIQR) for English, Afrikaans and Xhosa-speaking patients with FMS living in the Western Cape area of South Africa.

The following chapter presents the methodology and results of this study.

3.2 Methods and Materials

3.2.1 Ethical considerations

Ethical approval for this study was obtained from the Health Research Ethics Committee (HREC) of the Stellenbosch University (SU), South Africa, during July 2010. Permission to conduct the study was provided by the Committee for Postgraduate Education (CPE) of SU, South Africa. Permission to conduct the study at Tygerberg Hospital (TBH) was granted by the Western Cape Department of Health. Permission to cross-culturally adapt and validate the original versions of the outcome measures was obtained from the original developers of the outcome measures and/or the MAPI institute. All eligible subjects were required to read and sign an informed consent form prior to participating in the study (in their preferred language, English, Afrikaans or Xhosa). To ensure anonymity, a unique study identification number/code (i.e. VR01-01, VR01-02, etc.) was allocated to each subject on recruitment. Confidentiality of subject information and data was maintained by storing all study data in a locked, access-controlled facility.

3.2.2 Study objectives

The primary objectives of the following study were therefore to:

1) Cross-culturally adapt and translate the PCS, TSK and FIQR among a group of English, Afrikaans and Xhosa-speaking patients with FMS living in the Western Cape area of South Africa;

2) Develop the English, Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR; and

3) Ascertain the validity and reliability of the cross-culturally adapted English, Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR.

Secondary objectives of this study were to:

1) Establish the socio-demographic profile of the patients with FMS attending the TBH Rheumatology clinic;

2) Ascertain the prevalence of pain catastrophizing, fear-avoidance behaviours, impact of FMS and physical activity levels amongst patients with FMS registered at TBH using the SA-PCS, SA-TSK, SA-FIQR and GPPAQ respectively; and

3) Ascertain the exercise activities most commonly catastrophized by the patients with FMS at TBH, using a modification of the Photographic series of daily activities (PHODA) system.

3.2.3 Study setting

The study was conducted at the Rheumatology and Occupational therapy departments of TBH, an academic tertiary institution situated in the northern suburbs of the Cape Metropole area of the Western Cape, South Africa was granted by the Western Cape Department of Health. TBH is dedicated to providing healthcare services to people living in and around the Cape Metropole area, as well as people from the broader Western Cape area of South Africa.

3.2.4 Study design

This study incorporated a repeated-measures study design.

3.2.5 Sample size (estimated using power analysis)

The main objective of this study was to ascertain the validity of the cross-culturally adapted English, Afrikaans and Xhosa versions of the PCS. For internal consistency, the sample size required for this study was based on an ICC of 0.9 and a maximum width of 0.23 for the 95% CI. The expected ICC and width of the 95% CI was based on previous studies. The

formula used to calculate the sample size was N = [16p (1-p)]/w2 where p is the expected ICC and w is the width of the 95% CI.

Per language group (English, Afrikaans and Xhosa), the minimum sample size was calculated to be 27 subjects. The total sample was estimated to be 81 subjects.

3.2.6 Subject inclusion and exclusion criteria

Subject recruitment criteria included:

- Male and female adults aged 18 years and older;
- Patients clinically diagnosed with FMS according to the American College Rheumatology (ACR) criteria by a qualified rheumatologist;
- Patients with FMS registered at the TBH Rheumatology clinic;
- South African citizens;
- Patients with FMS who spoke, comprehended and were proficient in either the English, Afrikaans or Xhosa language;
- Patients with FMS who resided in and around the Cape Metropole area or the larger part of the Western Cape area of South Africa.

Eligible subjects were consecutively recruited into the study. Subjects who could not fully comprehend what the project entailed and what was expected of them, and for whom valid contact details were unavailable from the TBH Rheumatology clinic's database, were excluded.

3.2.7 Study instruments

3.2.7.1 Sociodemographic form

The form was specifically designed to collect data pertaining to sociodemographic information (i.e. age, gender, marital status, level of education, employment status, etc.) as

well as information pertaining to FMS pain/symptoms, severity of pain /symptoms, frequency of pain/symptoms, etc.) (Appendix 1).

3.2.7.2 Pain severity scale

Pain severity was measured using a simple 5-point Likert scale where “1” was “not bad at all” and “5” was ”unbearable” (Part of Appendix 1).

3.2.7.3 Pain catastrophizing scale (PCS)

A self-report measure, the PCS is a broad measure of pain catastrophizing and consists of 13 items scored using a 5-point Likert scale from 0 (never) to 4 (always). The total score for the PCS equals 52. Responses are summed to create a total score, with higher scores (>24) indicating greater pain catastrophizing levels. The items are divided into three subscales; namely *rumination, helplessness* and *magnification*. Rumination (items 8- 11) “refers to the fact that the patient cannot get the idea of pain out of his/her head and cannot stop thinking about the pain”; Helplessness (items 1-5 and 12) “refers to the estimation that the person has not been able to do anything to influence the pain”; and Magnification (items 6, 7 and 13) “refers to the exaggeration of the threatening properties of the painful stimulus”. High internal reliability (α for total PCS = 0.87) has been reported in patients with chronic pain with adequate validity and test-retest reliability (Sullivan et al., 1995).

3.2.7.4 Tampa scale for Kinesiophobia (TSK)

The TSK is a self-report instrument designed to assess fear of pain and activity. It consists of 17 items each rated on a 4-point Likert scale. The scores on items 4, 8, 12 and 16 are reversed. The scale consists of two factors namely: *Somatic Focus* (SF) (items 3, 5, 6, 7 and 11) and *Activity Avoidance* (AA) (items 1, 2, 9, 10, 13, 14, 15 and 17) (Roelofs et al., 2004). Total scores for the TSK range from 17 to 68. Responses are summed to create a total score, with higher scores (> 37) indicating greater fear of pain/(re)injury due to movement or

activities. The scale has demonstrated test-retest reliability and internal consistency (Cronbach alphas have ranged 0.68 to 0.80) in studies of patients with chronic low back pain. Stability over time and criterion validity and construct validity have been well established (Roelofs et al., 2004).

3.2.7.5 Revised Fibromyalgia Impact Questionnaire (FIQR)

The FIQR is an updated and shortened version of the FIQ that has good psychometric properties, can be completed in less than 2 minutes and is easy to score. It has scoring characteristics comparable to the original FIQ, making it possible to compare past FIQR results with future FIQR results (Bennett et al., 2009). The original FIQ was developed and validated by Burckhardt *et al*. (1991) to assess the current health status of women with FMS.

3.2.7.6 General Practice Physical Activity questionnaire (GPPAQ)

The GPPAQ is a validated screening tool for use in primary care to assess adult (16 – 74 years) physical activity levels (Physical Activity Policy, NHS., 2009). It provides a simple 4-level physical activity index, categorizing patients as inactive, moderately inactive, moderately active and active (Appendix 2).

3.2.7.7 Modified PHODA

The PHODA is a standardized method involving photographs representing various physical daily-life activities. For the project, exercise activities were used instead to compile a hierarchy of fear-eliciting movements and activities, and a modified version of the PHODA (Appendix 3) was created (Kugler et al., 1999). The purpose of the modified PHODA was to ascertain which exercise activities the subjects felt/thought would increase their pain/symptoms the most. The modified PHODA consisted of 12 pictures of different types of exercises. The exercises activities were as follows: *cycling, leg-lifts, aerobics, running, stretching, step-ups, treadmill walking, walking briskly, swimming, sit-ups, and tennis*. Each

picture contained a white block in the bottom right-hand corner. The subjects were instructed to take their time to look at each picture and then to imagine themselves doing the exercise activity shown in the picture. Subjects then had to mark all the pictures which they honestly felt they could not do because they thought it would cause them too much pain or make their symptoms worse. Subjects were allowed to mark as many pictures as they wished.

3.2.8 Study procedure

Eligible subjects were sampled from the available FMS population registered at the TBH's Rheumatology clinic, and those attending the FMS support group (hosted by the TBH's Occupational Therapy department) between October 2010 and December 2011. The rheumatologists and/or occupational therapist working at the clinic were requested to identify all new or previously diagnosed patients with FMS. In addition, the principal researcher and research assistant manually searched the clinic's database for any patient with FMS discharged from the clinic between 2009 and 2011. Patients were identified using the current ICD code for FMS, *M79.9*. All patients for whom contact details were available, and valid, were contacted telephonically and invited to participate in this study. A professional Xhosa translator assisted in collecting data from Xhosa- speaking participants. Remuneration for travelling to and from the study setting was provided. On recruitment into the study, the study procedure was thoroughly explained to each eligible subject and an informed consent form (Appendix 4) was signed in their preferred language. Information pertaining to sociodemographics; FMS pain/symptom severity and frequency; and general physical activity level was collected for all eligible subjects on recruitment using specifically designed forms.

3.2.8.1 Cross-cultural adaptation process

Cross-cultural adaptation of the original versions of the PCS, TSK and FIQR was performed in accordance with previously published guidelines (Guillemin et al., 1993; Beaton et al.,

2000). Two rheumatologists, one pain physiotherapist and two occupational therapists, knowledgeable in the field of FMS/rheumatology and working in the public/private sector were invited to form part of an expert committee and assist in the cross-cultural adaptation of the PCS, TSK and FIQR. A subgroup of ten patients with FMS currently attending the FMS support group hosted on a monthly basis by the TBH Occupational therapy department, were invited to participate in this preliminary process. The subgroup of patients with FMS consisted of five English-speaking, three bilingual English-Afrikaans speaking and two bilingual English-Xhosa speaking subjects. The original versions of the PCS, TSK and FIQR were sent to the panel members via email, and were personally administered to the subgroup of FMS subjects in a scheduled meeting. In a detailed letter, the panel members and subjects were specifically asked to carefully check if there were any items in the original versions of the PCS, TSK and FIQR which were not applicable to patients with FMS currently registered at the TBH Rheumatology clinic and living in South Africa. The panel members and subjects with FMS were also asked to suggest any changes which may deem the questions more applicable to the intended population. After the original versions of the PCS, TSK and FIQR had been reviewed and scrutinized by the panel members and the subgroup of FMS subjects, the principal researcher collated the suggested changes in MS Excel.

- ***Suggestions made by expert committee and patient subgroup***

All suggestions received by the expert committee and patient subgroup were collated into the main ideas and listed for each outcome measure per aspect of the questionnaire (instructions, wording of items, scoring system and structure) in table 3.1. Based on the suggestions and comments received by the expert committee and the subgroup of patients with FMS, the following modifications were made to the overall layout/structure, the instructions, the scoring system, and wording of the items of the original versions of the

PCS, TSK and FIQR to make them more culturally applicable for South African patients with FMS:

- ***Modifications to the PCS***

The instructions on how to complete the PCS were revised and simplified, and the section pertaining to the statement regarding individual pain experiences was removed. For the purpose of this validation study, the section pertaining to personal information was removed and replaced with a section for the study identification number and the date. The anchors "*not at all", "to a slight degree", "to a moderate degree", "to a great degree" and "all the time"* were retained in the adapted version of the PCS. However, since patients found it difficult to understand and apply the original scoring system, modifications were made to the layout of the form by placing tick boxes next to each question individually for the anchors. Patients were therefore required to place their responses using an 'X' in the appropriate box. The score for each anchor remained the same as the original PCS, ranging from "0" for "*not at all*" to "4" for "*all the time*". A number of changes were made to the wording of the items based on the suggestions made by the expert committee and the patient group. In the original PCS, the words "*When I'm in pain…*" is placed at the top of the item list and is required to be applied to each item individually. Patients in this sample, however, had difficulty understanding this concept. A modification was therefore implemented whereby the words "*When I'm in pain…"* was placed before each item individually.

- ***Modifications to the TSK***

The original TSK does not include instructions on how to complete the questionnaire. Instructions on to how to complete the questionnaire was therefore included to ensure that subjects understood what was expected of them. For the purpose of this validation study, a section for the study identification number and the date was included. The anchors "*strongly disagree"; "disagree"; "agree" and "strongly agree*" were retained in the adapted version of the TSK. The scores for each anchor remained the same as the original TSK, ranging from "1" for "*strongly disagree*" to "4" for "*strongly agree*". However, since patients found it difficult

to understand and apply the original scoring system, modifications were made to the layout of the form by placing the anchors directly above the corresponding score column making it easier for patients to apply the scoring system by placing their responses using an 'X' in the appropriate box.

- ***Modifications to the FIQR***

The instructions on how to complete the FIQR were revised and simplified. For the purpose of this validation study, the section pertaining to personal information was removed and replaced with a section for the study identification number and the date. From the suggestions made by the expert committee it was decided that the unnumbered sliding scales used in the original FIQR may be difficult for some patients to apply. To make scoring even easier, the scoring system for each subsection of the FIQR was altered. In subsection 1, the unnumbered sliding scale was changed to a Likert-scale with 5 anchors: "*no difficulty at all"; "little difficulty"; "difficult"; "quite difficult";* and "*extremely difficult"*. A tick box was placed next to each of the nine items individually in subsection 1 for each anchor. The total score for subsection 1 was 90 with the scores for each anchor equaling "2" for "*no difficulty at all*"; "4" for "*little difficult*"; "6" for "*difficult*"; "8" for "*quite difficult*" and "10" for "*extremely difficult*". In subsection 2, again the unnumbered sliding scale was changed to a Likert-scale with 4 anchors: *"never; sometimes; most times;* and *always*". A tick box was placed next to each of the two items individually in subsection 2 for each anchor. The total score for subsection 2 was 20 with the scores for each anchor equaling "2.5" for *"never";* "5" for "*sometimes; "*7.5" for *most times;* and "10" for *always*". In subsection 3; the unnumbered sliding scale was changed to a Likert-scale with 5 anchors for each item. The total score for subsection 3 was 100, with the anchors scoring 2, 4, 6, 8 or 10, respectively. The total score of the FIQR remained 210 points.

Table 3.1: Suggestions made by expert committee

Level	PCS	TSK	FIQR
Overall	*"Despite its usefulness, it seems similar and will need careful translation and cognizance of colloquialisms (eg. Worried vs stresses. Translation also need to include " thinking about xyz…"*	*Overall: "generally illustrates thought processes well"*	
Instructions	*"would suggest that the instructions are simplified…"*	*"the instructions may be too difficult for patients who have a low-educational level, should perhaps simply this…"*	
Wording/Structure			
Items	*Item 1: translation should clearly indicate that "it will end" and not just focus on continual worry…"; Item 4: "Difficult to differentiate between these two translations"; Item 7: "I keep thinking of other painful events" sounds ambiguous…"; Item 8: "not sure, difficult sentence – can 'stresses' perhaps be used in it?*	*Item 2: "very abstract, may need explanation…"; "vaguely put…"; "…not sure what is meant by 'accident'…"*	*Functional subscale: "clear activities that may differ depending on whether patients have access to public/private transport for shopping, etc. Symptom subscale: "…tenderness to touch may be confused with pain response when translated"; "use of energy is confounded with cultural aspects…"*
Scoring system	*May be difficult to apply scoring system if patient has low education*	*May be difficult to apply scoring system if patient has low education*	*"Use of unnumbered sliding scale is difficult for patients with low-educational levels"*

3.2.8.2 Forward- and back translation process

A professional and independent freelance Afrikaans and Xhosa translator and a native Afrikaans- and Xhosa-speaking health professional were consulted for English to Afrikaans and Xhosa forward-translation of the adapted English SA-PCS, SA-TSK and SA-FIQR to ensure that all changes suggested during the cross-cultural adaptation process were incorporated into the Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR. The translators were not informed of the project details. The translators were asked to compare the translated Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR to the original PCS, TSK and FIQR. The translated Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR were forwarded to two professional Afrikaans and Xhosa translators who independently and blindly performed back translations of the Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR into English. The English SA-PCS, SA-TSK and SA-FIQR was not supplied to the back translators as a reference. Following professional forward- and back-translation of the English SA-PCS, SA-TSK and SA-FIQR to Afrikaans and Xhosa, as well as professional editing of all the documents, the pre-final versions of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR were produced for further testing of the following psychometric properties, namely: *face and content validity, internal consistency, test-retest reliability, sensitivity-to-change* and *cross-sectional convergent validity*.

3.2.8.3 Validity and reliability testing

3.2.8.3.1 Acceptability and comprehensibility testing (Face and content validation)

The pre-final versions of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR were tested among a second subgroup of FMS subjects to establish face and content validity (acceptability and comprehensibility). The subjects were given the SA-PCS, SA-TSK and SA-FIQR in their preferred language. The purpose of this procedure was to ensure that the cross-culturally adapted and translated versions of the SA-PCS, SA-TSK and SA-FIQR

were understood within the local context and in the provided languages, and that the items measured what they were intended to measure. A subgroup of 24 subjects (eight English-; nine Afrikaans-; and seven Xhosa-speaking) were invited to test the pre-final versions of the adapted English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR. The subjects had the opportunity to scrutinize the content of the cross-culturally adapted and translated versions of the SA-PCS, SA-TSK and SA-FIQR and comment on the ease of completing the questions. The subjects were asked questions based on their understanding of the instructions provided; the ease of understanding the questionnaire in their language; the ease of completing the questionnaire; and if sufficient time was provided to complete the questionnaire. The comments and suggestions made by the patients were collated and evaluated.

3.2.8.3.2 Internal consistency and test-retest

The final SA-PCS, SA-TSK and SA-FIQR were administered to the final group of eligible FMS subjects in their preferred language (English, Afrikaans or Xhosa). Reliability of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR was tested by means of internal consistency and test-retest reliability. Internal consistency relates to the homogeneity of the scale. Test-retest reliability measures stability over time/reproducibility, by administering the same test to the same subject at two points in time. To measure test-retest reliability of the cross-culturally adapted and translated SA-PCS, SA-TSK and SA-FIQR, subjects were required to complete two forms at different time points. After completing the first SA-PCS, SA-TSK and SA-FIQR, subjects were asked to return to the study setting within one month and complete a second form.

3.2.8.3.3 Sensitivity-to-change

Sensitivity-to-change is “the capacity of a measure to detect change in patients over time” and relates to the “clinical meaningfulness of changes in scores” (Stratford et al 1998; Riddle

et al., 1998). Sensitivity-to-change is indicated by the minimum detected change (MDC) score which is “the degree of change required in an individual’s score to ascertain if the change is real, over and above measurement error” (Stratford et al., 1998).

3.2.8.3.4 Cross-sectional convergent validity

Cross-sectional convergent validity is defined as “the extent to which the scores of the measurement of interest relate to other measures in an expected manner” (DeVon et al., 2007). Usually, the adapted measure is correlated with a related measure which has been previously validated in a similar population or ‘gold standard’. However, since no related outcome measure has been previously validated in a South African FMS population, the scores of the adapted SA-PCS, SA-TSK and SA-FIQR were correlated to each other and to pain severity. It was hypothesized that the adapted and translated English, Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR would measure scores relative to each other and to pain severity.

3.2.9 Statistical analysis

Data were collated, extracted and entered into a purpose-built MS Excel worksheet. Incomplete or incorrectly completed SA-PCS, SA-TSK and SA-FIQR forms were considered and analyzed accordingly. Open-ended responses collected during the face and content validity testing were coded and qualitatively analyzed. Internal consistency of the final cross-culturally adapted and translated SA-PCS, SA-TSK and SA-FIQR were estimated using the Cronbach’s alpha (α) that ranges from 0-1. The “reliability calculator” developed by Siegle (2005) (a web-based reliability calculator) was used to calculate the Cronbach’s α estimates for the subsections of the SA-PCS (rumination, helplessness and magnification) and the total SA-PCS; the subsections (activity avoidance and somatic focus) of the SA-TSK and the total SA-TSK; and the subsections (functional, impact and symptoms) and the total SA-FIQR. The

internal consistency was estimated for each language version of the SA-PCS, SA-TSK and SA-FIQR separately and as a whole.

To evaluate test-retest reliability, intraclass correlation coefficient (ICC) and 95% confidence intervals (CIs), as well as standard error of measurement (SEM) were estimated. The ICC is "an index of the reliability of the measurements between tests"(Müller et al., 1994). One-way ANOVA's were conducted to calculate the within-subject variance. These variances were used to calculate the ICC using the formulae: ***ICC = Subject variance/Subject variance + Error.*** The SEM "estimates how repeated measures on the same instrument tend to be distributed around the "true" score" (Brown et al., 1999) and is calculated using the formula: ***SEM = SD √1-r.*** ICC values of 0.60 to 0.80 were regarded as evidence of good reliability, and those of higher than 0.80 were considered as excellent reliability (Mousavi et al., 2006). The higher the coefficient value, the higher the reliability and the lower the SEM. To establish sensitivity-to-change, the estimated SEM was used to calculate the MDC using the formulae: ***MDC = 1.96 x √2 x SEM.*** Pearson correlation coefficients (*r*) were used to measure cross-sectional convergent validity between the adapted and translated versions of the PCS, TSK and FIQR. Student's t-tests were used to estimate the significance of correlations and differences in test-retest scores. Statistical significance was accepted at $p < 0.05$. Descriptive statistics (means and standard deviations (SD)) were used to analyze data collected pertaining to socio-demographic information, FMS symptoms and general physical activity levels.

3.3 Results

A total of 154 patients, diagnosed with FMS and registered at the TBH Rheumatology clinic between June 2009 and December 2011, were identified either by the rheumatologists working in the clinic or via a search of the clinic's database. Figure 3.1 illustrates the inclusion and exclusion process of subjects.

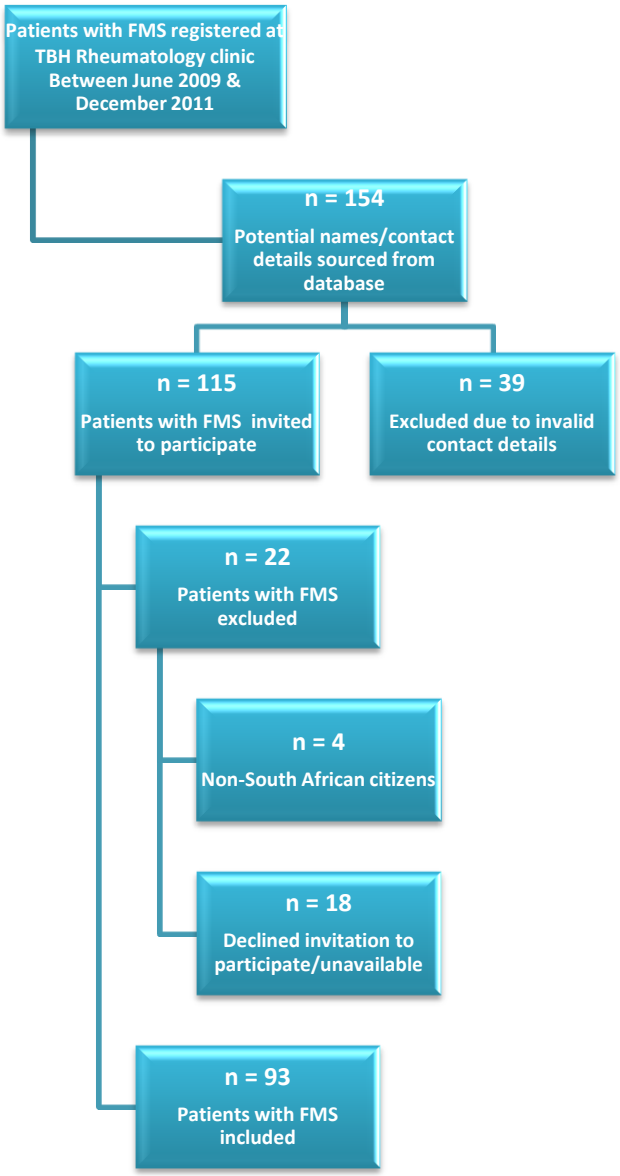


Figure 3.1: Consort diagram depicting subject inclusion and exclusion process

3.3.1 Subject sociodemographic information

Ninety-three eligible subjects with FMS (89 females and 4 males) were included in this study. The ethnic groups included “coloured” (n=68; 73.1%); “black” (n=19; 20.4%); “white” (n=4; 4.3%) and “other” (n=2; 2.2%). Figure 3.2 depicts the distribution of ethnicity among the study sample.

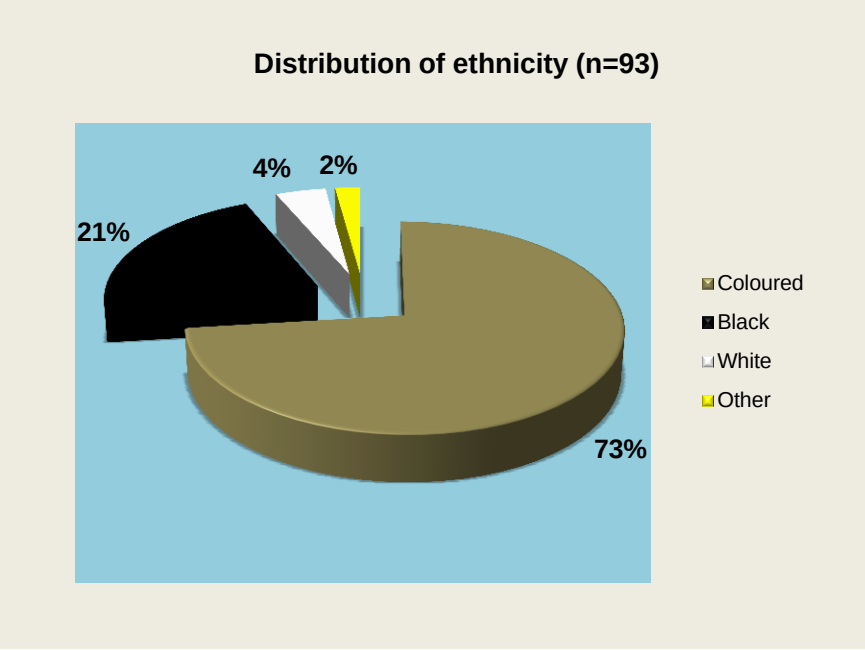


Figure 3.2: Distribution of ethnicity among total sample of study subjects (n=93)

The mean±SD age for the subjects was 47.28±10.38 years. The mean±SD number of years living with FMS was 5.37±4.88 years. The mean number of children was 3±1. Table 3.2 illustrates the demographics of the subjects per age, number of children, smoking status, etc.

Table 3.2: Socio-demographic characteristics of included subjects

Variable	N (%)	Mean±SD
Age (yrs)	93 (100)	47.28±10.38
Female	89 (95.7)	47.76±10.31
Male	4 (4.3)	36.5±4.72
Coloured	68 (73.1)	47.53±9.81
Black	19 (20.4)	42.79±9.67
White	4 (4.3)	58.50±12.37
Other	2 (2.1)	59.00±12.73
No. of children	93 (100)	2.71±0.95
Female	89 (95.7)	2.73±0.96
Male	4 (4.3)	2.33±0.57
Coloured	68 (73.1)	2.75±0.92
Black	19 (20.4)	2.41±1.06
White	4 (4.3)	3.25±0.96
Other	2 (2.1)	3.00±0.00
No. of years living with FMS	93 (100)	5.37±4.65
Female	89 (95.7)	5.48±4.73
Male	4 (4.3)	3.00±0.00
Coloured	68 (73.1)	4.75±2.91
Black	19 (20.4)	6.16±6.18
White	4 (4.3)	5.00± 3.6
Other	2 (2.1)	18.50±16.26
Smoking?	92 (98.9)	
Yes	34 (36.9)	
No	58 (63.0)	
Previous alcohol/drug abuse	91 (93.5)	
Yes	8 (8.8)	
No	83 (91.2)	
Institutionalized?	87 (93.5)	
Yes	2 (2.3)	
No	85 (97.8)	
Drug usage	93 (100)	
Anti-depressants	21 (22.6)	
Analgesics	72 (77.4)	
Muscle relaxants	22 (23.6)	
Other	17 (19.4)	
None	12 (12.9)	
Allied health services utilization	93 (100)	
Physiotherapy	52 (55.9)	
Occupational Therapy	67 (73.1)	
Psychology/Psychiatry	22 (23.7)	
Reflexology	2 (2.2)	
Acupuncture	2 (2.2)	
Co-morbidities (primary)	93 (100)	
Hypertension	37 (39.8)	
Diabetes Mellitus (NIDDM)	14 (15.1)	
Chronic Heart Disease	8 (8.6)	
Chronic Lung Disease	3 (3.2)	
Chronic Liver/Bladder/Kidney Disease	2 (2.2)	
Epilepsy	2 (2.2)	
Systemic Lupus Erythematosus (SLE)	1 (1.1)	
Cancer	1 (1.1)	
HIV/AIDS	1 (1.1)	
Bipolar disorder	1 (1.1)	
None	21 (22.6)	

Of the 93 subjects included in this study, 41 (44.1%) were Afrikaans-speaking, 33 (35.5%) were English-speaking and 19 (20.4%) were Xhosa-speaking. Figure 3.3 depicts the distribution of ethnicity per language group.

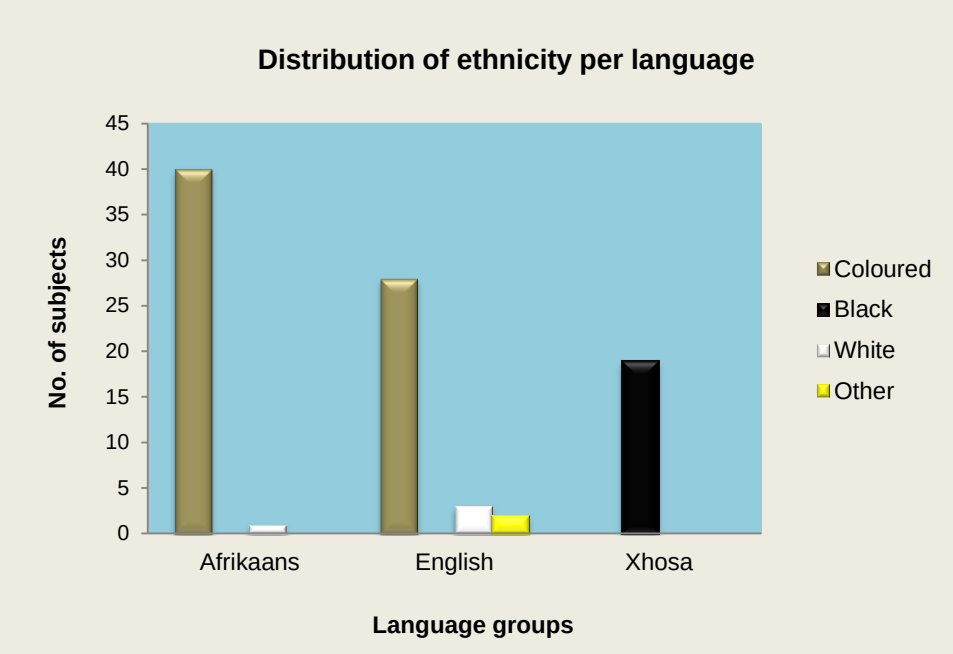


Figure 3.3: Distribution of ethnicity per language group

The majority of the included subjects were from the *Cape Flats* area (n=66; 76.1%). Figure 3.4 depicts the distribution of ethnicity per area/suburb. Figure 3.5 depicts the number of subjects per area/suburb.

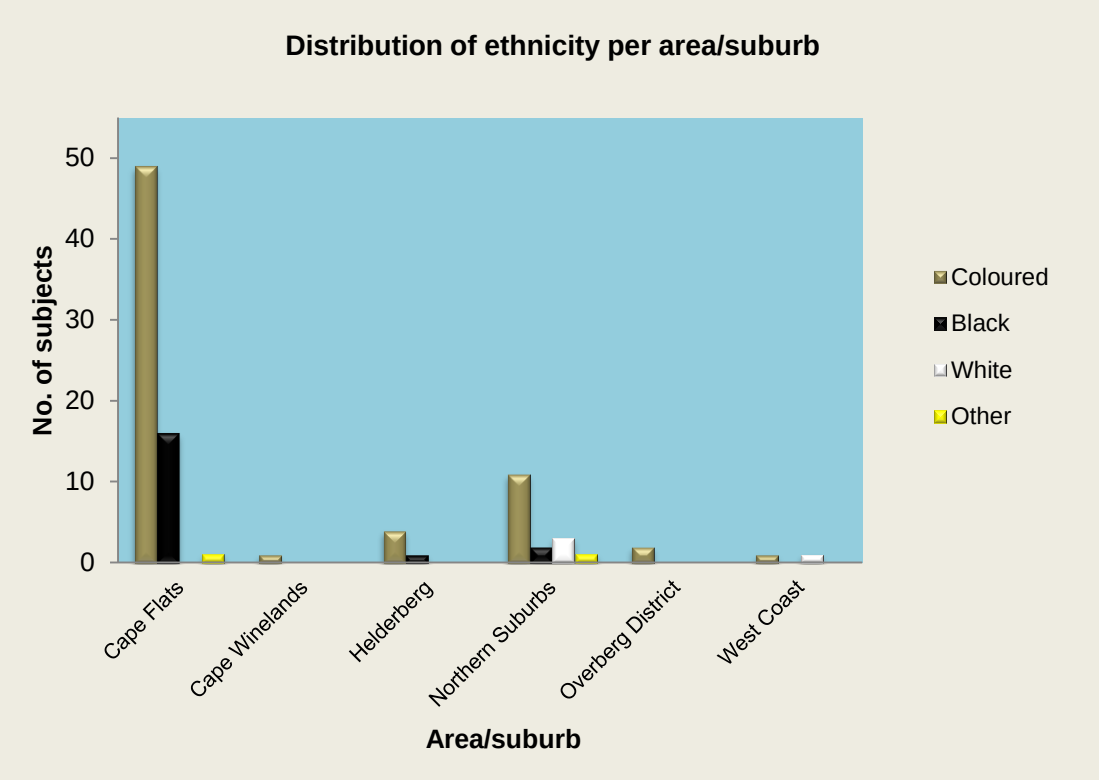


Figure 3.4: Distribution of subjects per area/suburb

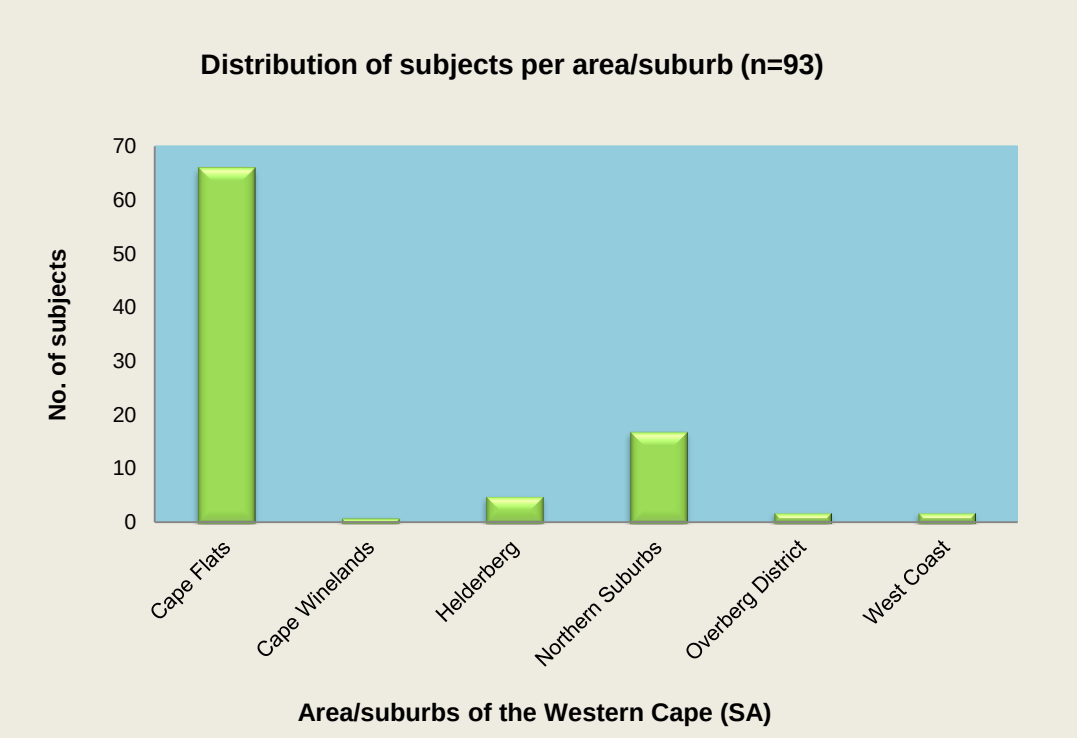


Figure 3.5: Distribution of subjects per area/suburb

Thirty-four (36.6%) subjects were married. Figure 3.6 depicts the distribution of ethnicity per marital status, *"single; married; separated; divorced* and *widowed".*

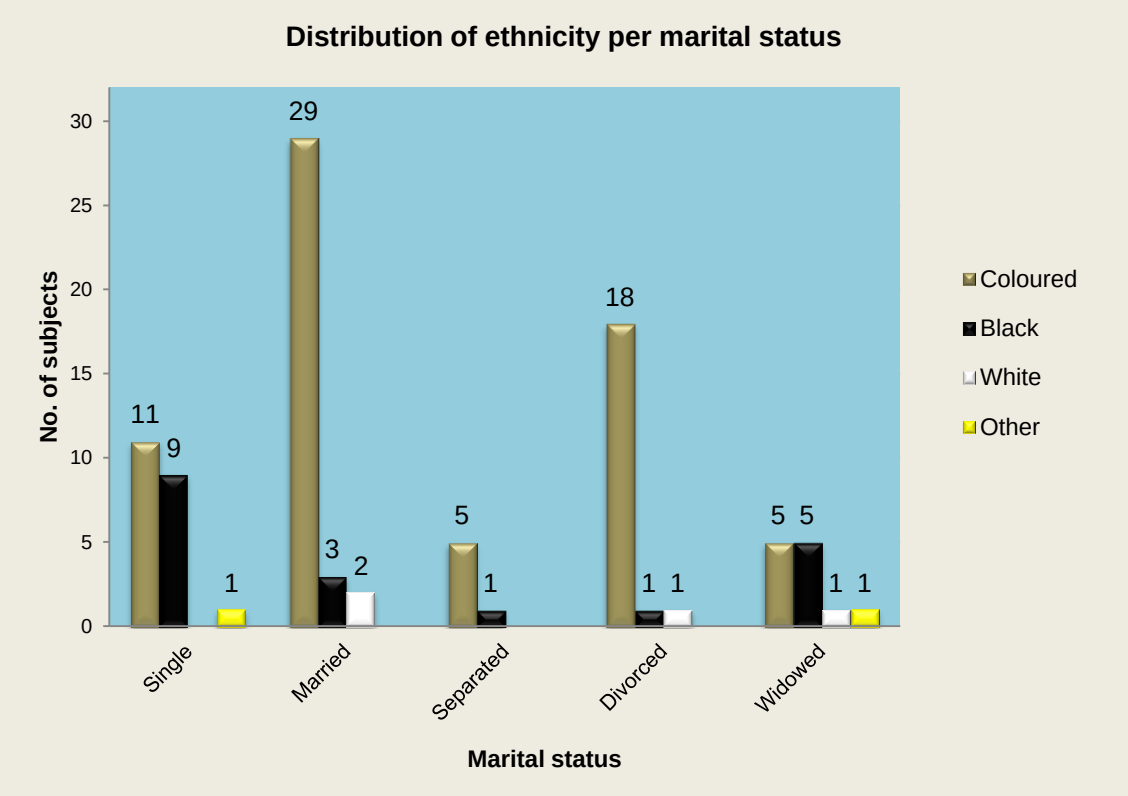


Figure 3.6: Distribution of ethnicity per marital status

The highest level of education for the majority of the subjects (n=38; 40.9%) was reported as *lower than grade 12*. Figure 3.7 illustrates the distribution of languages and ethnic group for each educational level category: *"lower than grade 7; grade 7; lower than grade 12; grade 12* and *tertiary education".*

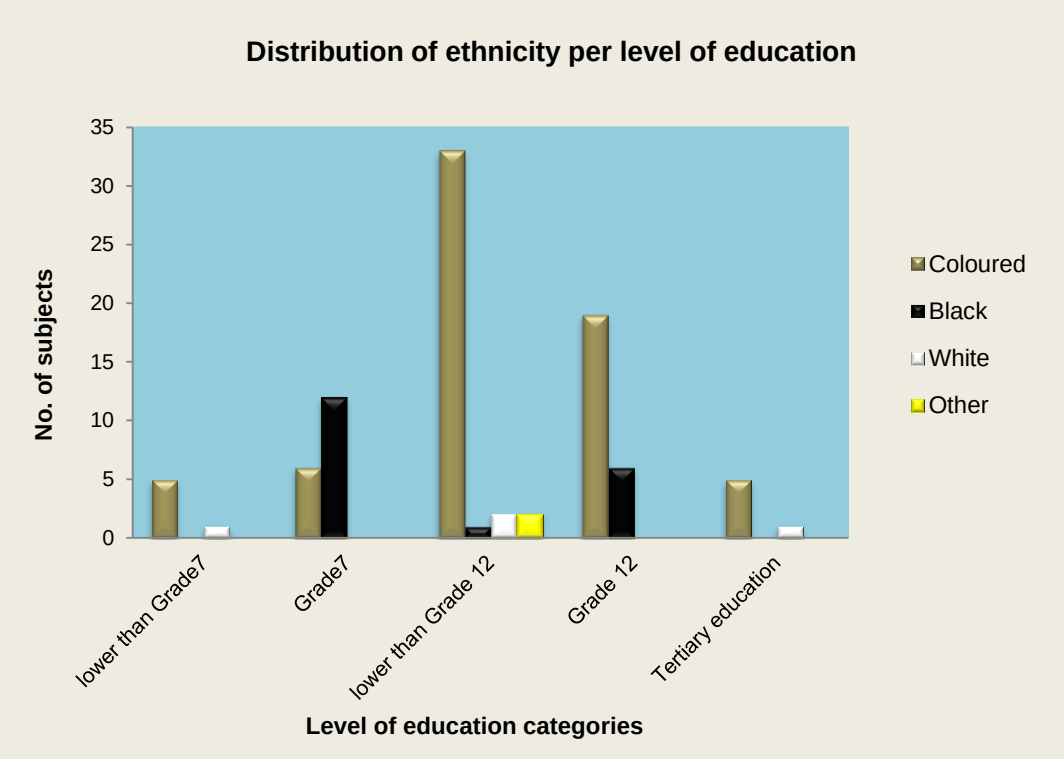


Figure 3.7: Distribution of ethnicity per education level

The majority of subjects reported to be unemployed (n=32; 34.4%). Of those reported as "unemployed", 17 (53.1%) were "coloured" and 14 (43.8%) were "black". Figure 3.8 depicts the distribution of ethnicity per employment status.

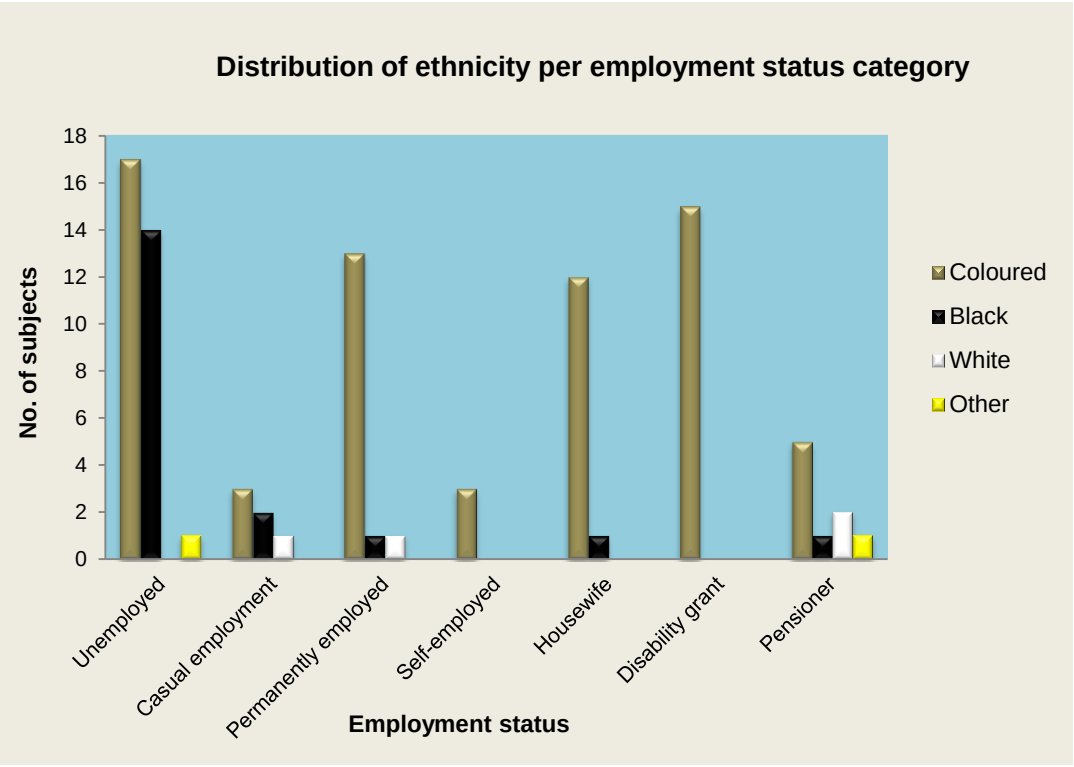


Figure 3.8: Distribution of ethnicity per employment status

3.3.2 Patient self-reported outcomes

3.3.2.1 Pain/symptom severity and frequency

Severity (measured as “not at all”; “mild”; “moderate”; “severe” and “unbearable”) of pain and symptoms related to FMS were reported. Figure 3.9 depicts the distribution of subjects per severity of FMS pain/symptoms category. Frequency (measured as “all the time”; “everyday”; “every second day”; “2 to 3 times per week” and “once a week”) of pain and symptoms related to FMS were reported. Figure 3.10 illustrates the distribution of frequency of FMS pain/symptoms among the included subjects.

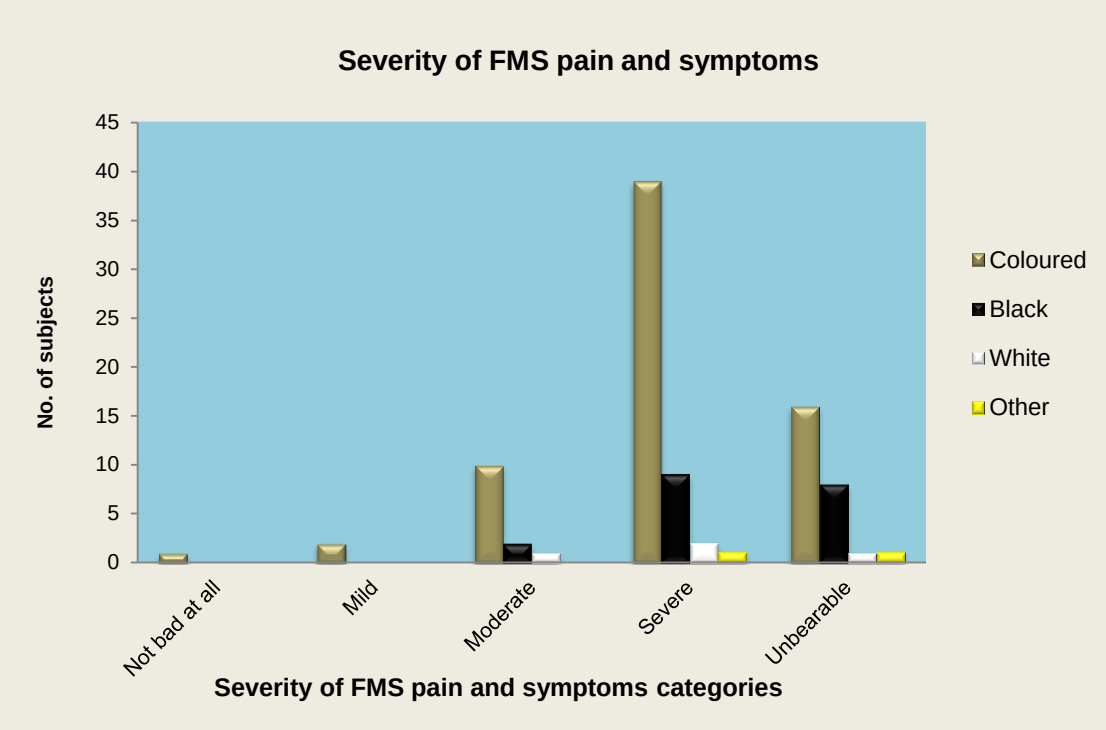


Figure 3.9: Distribution of ethnicity per severity of pain/symptoms category

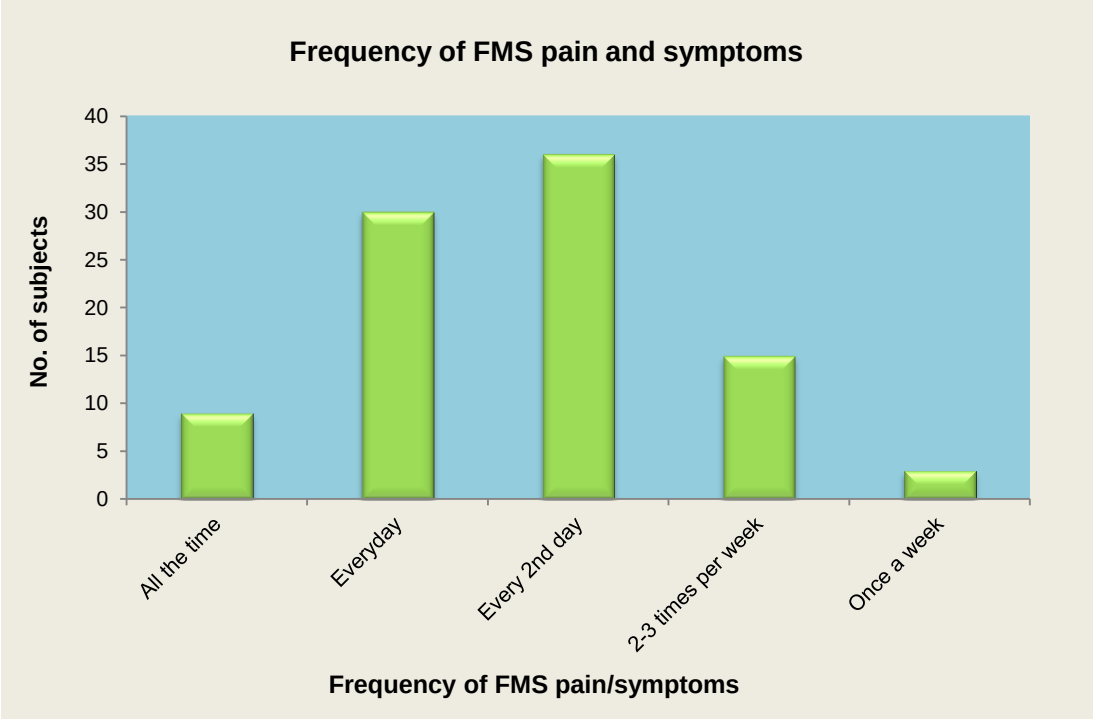


Figure 3.10: Distribution of frequency of FMS pain and symptoms

3.3.2.2 Levels of pain catastrophization, kinesiophobia, and impact of FMS

Pain catastrophization was measured using the adapted SA-PCS. Levels of kinesiophobia were measured using the adapted SA-TSK. The impact of FMS was measured using the adapted SA-FIQR. In table 3.3, the mean±SD scores of the SA-PCS, SA-TSK and SA-FIQR per ethnic and language group are illustrated.

Table 3.3: Patient self-reported outcome measures per ethnic and language group

Language/ ethnic group	N	SA-PCS Mean±SD Max score: 52	SA-TSK Mean±SD Max score: 68	SA-FIQR Mean±SD Max score: 210
Afrikaans	**41**	**36.05±11.21**	**51.63±6.68**	**135.60±22.77**
Coloured	40	36.23±11.29	51.656.77	135.36±23.01
White	1	29.00±0.00	51.00±0.00	145.00±0.00
English	**33**	**38.03±10.37**	**51.88±5.20**	**142.91±20.17**
Coloured	28	37.39±10.50	51.21±4.85	141.73±20.66
White	3	36.67±9.71	54.00±7.00	151.67±23.50
Other	2	49.00±4.24	58.00±5.66	146.25±9.55)
Xhosa	**19**	**34.16±8.45**	**47.11±7.19**	**142.53±23.44**
Black	19	34.16±8.45	47.11±7.19	142.53±23.44
Total	**93**	**36.37±10.40**	**50.80±6.52**	**139.61±22.07**
Total Coloured	**68**	**36.71±10.91**	**51.47±6.02**	**137.99±22.14**
Total Black	**19**	**34.16±8.45**	**47.11±7.19**	**142.53±23.44**
Total White	**4**	**34.75±8.81**	**53.25±5.91**	**150.00±19.48**
Total Other	**2**	**49.00±4.24**	**58.00±5.66**	**146.25±9.55**

3.3.2.3 General physical activity

Physical activity levels were measured using the GPPAQ. The mean±SD hours the subjects spent on physical activity per week was 10.71±7.07. Thirty-one subjects reported that their walking pace was “average” (63.2%); 14 reported their walking pace as “slow” (28.6%); 3 reported their walking pace as “very slow” (6.7%); and 1 reported their walking pace/speed as “fast”. The most common classification of work reported was “not working” (n=38; 77.6%). Four reported their work involved “sitting most of the day”; two reported that they “drove most of the day”; three reported that they “stood most of the day”; and two reported that their work involved medium and heavy duty, respectively.

3.3.2.4 Exercise activities reportedly feared

Of the 12 exercise activities represented in the modified PHODA, the following were most frequently reported as feared: *cycling, leg-lifts, aerobics, running, stretching, treadmill walking, sit-ups and tennis*.

3.3.3 Psychometric testing of outcome measures

3.3.3.1 Subjects

Figure 3.11 illustrates the number of subjects participating at each phase (pre-final and final phases) of the validation study.

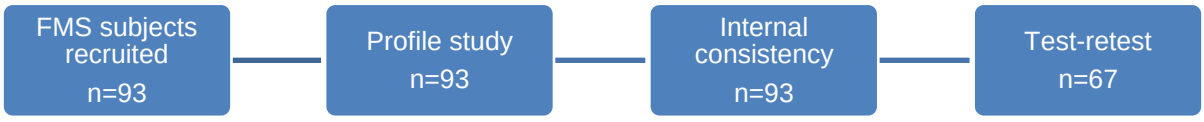


Figure 3.11: Subject participation in validation study

3.3.3.2 Acceptability and comprehensibility testing (Face and content validation)

The subgroup of 24 English-, Afrikaans- and Xhosa-speaking patients with FMS who participated in the face/content validation part of this study all reported that they understood the instructions provided; that the questionnaire was simple to complete; that the questionnaire was easy to understand in their language; that they understood what was meant by each question and that they were given enough time to complete the questionnaires. No further changes to the adapted English, and translated Afrikaans and Xhosa versions of the PCS, TSK and FIQR were therefore required. The final versions of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR were produced and further validated.

3.3.3.3 Internal consistency

Internal consistency was conducted among 93 subjects with FMS. Internal consistency of the adapted English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR was evaluated by calculating the Cronbach's α for the subsections and the total SA-PCS, SA-TSK and SA-FIQR, and are depicted in Tables 3.4 (a-c).

3.3.3.4 Test-retest reliability

Of the 93 subjects included in this study, 67 subjects (26 Afrikaans-; 22 English- and 19 Xhosa-speaking) completed two sets of the SA-PCS, SA-TSK and SA-FIQR in their preferred language, one month apart and were included in the test-retest analysis (see figure 3.10). The ICC's (95% CIs) and mean differences (MD) were calculated to establish test-retest reliability for the subsections and total English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR and are depicted in tables 3.5 (a-c). No significant differences were found between the test-retest total and subsection scores of the English, Afrikaans and Xhosa SA-PCS and SA-TSK. Significant differences were however found between the test-retest total scores of the Afrikaans SA-FIQR and the test-retest subsection (functional) scores of the English SA-FIQR.

Table 3.4(a): Cronbach's α values for English, Afrikaans and Xhosa SA-PCS (subsections and totals)

SA-PCS	N	Rumination α	Helplessness α	Magnification α	Total SA-PCS α
Afrikaans SA-PCS	41	0.996	0.984	0.985	0.984
English SA-PCS	33	0.990	0.982	0.961	0.981
Xhosa SA-PCS	19	0.986	0.949	0.932	0.970

Table 3.4(b): Cronbach's α values for English, Afrikaans and Xhosa SA-TSK (subsections and totals)

SA-TSK	N	Activity avoidance α	Somatic Focus α	Total SA-TSK α
Afrikaans SA-TSK	41	0.933	0.933	0.961
English SA-TSK	33	0.889	0.904	0.940
Xhosa SA-TSK	19	0.929	0.919	0.965

Table 3.4(c): Cronbach's α values for English, Afrikaans and Xhosa SA-FIQR (subsections and totals)

SA-FIQR	N	Functional α	Impact α	Symptoms α	Total SA-FIQR α
Afrikaans SA-FIQR	41	0.925	0.904	0.934	0.941
English SA-FIQR	33	0.934	0.912	0.942	0.946
Xhosa SA-FIQR	19	0.922	0.891	0.912	0.932

Table 3.5 (a) Estimates for test-retest reliability (ICC) of the SA-PCS

SA-PCS	N	Max score	PCS Test Mean±SD	PCS Retest Mean±SD	MD *t2-t1	ICC (95% CIs)	SEM	MD C	*P*
Afrikaans SA-PCS	26	**52**	**37.00±11.36**	**36.77±11.32**	**-0.23**	**0.91 (0.81-0.96)**	**3.26**	**9.03**	**0.71**
Rumination		16	10.21±3.63	10.36±3.64	0.15	0.88/(0.75-0.94)	1.71	4.74	0.24
Helplessness		24	17.86±5.03	17.87±4.86	0.01	0.87 (0.74-0.94)	1.75	4.85	0.36
Magnification		12	8.21±2.87	8.36±2.85	0.15	0.86 (0.72-0.94)	1.06	2.94	0.37
English SA-PCS	22	**52**	**38.23±11.49**	**39.05±11.54**	**0.82**	**0.91 (0.78-0.96)**	**3.19**	**8.84**	**0.93**
Rumination		16	10.35±3.50	10.42±3.58	0.07	0.88 (0.71-0.94)	1.20	3.32	0.77
Helplessness		24	18.15±4.90	18.05±4.73	-0.10	0.87 (0.79-0.92)	1.74	4.82	0.68
Magnification		12	8.43±2.73	8.52±2.70	0.09	0.86 (0.70-0.94)	0.99	2.77	0.57
Xhosa SA-PCS	19	**52**	**34.16±8.45**	**32.89±8.75**	**-1.27**	**0.89 (0.74-0.96)**	**3.34**	**9.25**	**0.79**
Rumination		16	10.45±3.48	10.65±3.54	0.20	0.88 (0.71-0.95)	1.23	3.41	0.37
Helplessness		24	18.21±4.80	18.06±4.57	-0.15	0.86 (0.67-0.94)	1.75	4.85	0.59
Magnification		12	8.44±2.68	8.55±2.60	0.11	0.84 (0.63-0.93)	1.06	2.94	0.52

*t2-t1 = mean difference between test and retest scores; ICC = intraclass correlation coefficient; SEM = standard error of measurement; MDC = minimum change difference; MD = mean difference; 95% CIs = 95% confidence intervals

Table 3.5 (b): Estimates for test-retest reliability (ICC) of the SA-TSK

SA-TSK	N	Max score	TSK Test Mean (SD)	TSK Retest Mean (SD)	MD *t2-t1	ICC (95% CIs)	SEM	MD C	*p*
Afrikaans SA-TSK	26	**68**	**50.36±6.53**	**50.39±6.72**	**0.03**	**0.81 (0.62-0.91)**	**2.85**	**7.89**	**0.95**
Activity avoidance		32	25.30±3.11	25.29±3.01	-0.01	0.85 (0.69-0.93)	1.20	3.33	0.95
Somatic focus		20	17.77±2.41	17.79±2.55	0.02	0.76 (0.53-0.88)	1.76	4.88	0.93
English SA-TSK	22	**68**	**50.71±6.61**	**50.72±6.73**	**0.01**	**0.82 (0.62-0.92)**	**2.80**	**7.76**	**0.89**
Activity avoidance		32	25.49±3.19	25.48±3.44	-0.01	0.80 (0.58-0.91)	2.06	5.71	0.95
Somatic focus		20	17.85±2.42	17.84±2.55	-0.01	0.82 (0.62-0.92)	1.03	2.86	0.99
Xhosa SA-TSK	19	**68**	**50.73±6.17**	**50.79±6.32**	**0.06**	**0.83 (0.61-0.93)**	**2.54**	**7.04**	**0.97**
Activity avoidance		32	25.40±3.02	25.48±3.15	0.08	0.79 (0.53-0.91)	2.02	5.59	0.75
Somatic focus		20	17.94±2.22	17.95±2.38	0.01	0.82 (0.62-0.92)	0.94	2.61	0.93

*t2-t1 = mean difference between test and retest scores; ICC = intraclass correlation coefficient; SEM = standard error of measurement; MDC = minimum change difference; MD = mean difference; 95% CIs = 95% confidence intervals

Table 3.5 (c): Estimates for test-retest reliability (ICC) of the SA-FIQR

SA-FIQR	N	Max score	FIQR Test Mean±SD	FIQR Retest Mean±SD	MD *t2-t1	ICC (95% CIs)	SEM	MDC	*p*
Afrikaans SA-FIQR	26	**210**	**140.29±21.77)**	**147.18±22.36**	**6.89**	**0.87 (0.73-0.94)**	**7.85**	**21.76**	**0.04†**
Functional		90	56.89±14.24	58.97±14.53	2.08	0.81 (0.62-0.91)	6.21	17.21	0.06
Impact		20	13.94±3.77	13.97±3.70	0.03	0.85 (0.69-0.93)	1.46	4.05	0.90
Symptoms		100	69.45±8.14	70.24±8.75	**0.79**	0.86 (0.71-0.93)	3.05	8.45	0.16
English SA-FIQR	22	**210**	**141.13±22.03**	**143.75±22.87**	**2.62**	**0.88 (0.73-0.95)**	**7.63**	**21.15**	**0.06**
Functional		90	57.06±14.37	59.20±14.04	2.14	0.84 (0.65-0.93)	4.98	13.80	0.04†
Impact		20	14.04±3.72	13.99±3.67	-0.05	0.85 (0.67-0.93)	1.44	3.99	0.85
Symptoms		100	70.03±8.40	70.55±9.04	0.52	0.88 (0.73-0.95)	2.91	8.07	0.32
Xhosa SA-FIQR	19	**210**	**142.33±20.11**	**144.90±20.85**	**2.57**	**0.85 (0.65-0.94)**	**7.79**	**21.59**	**0.08**
Functional		90	57.79±13.87	59.71±14.05	1.92	0.79 (0.53-0.91)	6.36	17.63	0.10
Impact		20	14.31±3.54	14.23±3.56	-0.08	0.84 (0.63-0.94)	1.42	3.94	0.73
Symptoms		100	70.23±7.45	70.97±8.21	0.74	0.83 (0.61-0.93)	3.07	8.51	0.21

*t2-t1 = mean difference between test and retest scores; ICC = intraclass correlation coefficient; SEM = standard error of measurement; MDC = minimum change difference; MD = mean difference; 95% CIs = 95% confidence intervals

3.3.3.5 Sensitivity to change

The MDC were calculated for the SA-PCS, SA-TSK and SA-FIQR as a whole and for the subsections, to establish the smallest change needed in scores to reflect a true change rather than measurement error. The values are depicted in Table 3.5 (a-c). The MDC for the English, Afrikaans and Xhosa SA-PCS, as a whole, was 8.84, 9.03 and 9.25, respectively. The MDC for the English, Afrikaans and Xhosa SA-TSK, as a whole, was 7.89, 7.76 and 7.04 respectively. The MDC for the English, Afrikaans and Xhosa SA-FIQR, as a whole, was 21.76, 21.15 and 21.59 respectively.

3.3.3.6 Cross-sectional convergent validity

The scores of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR were correlated to the scores of pain severity (5-point Likert scale) and each other. The Pearson's correlation coefficients (*r*) produced between the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR as well as pain severity scores are depicted in Table 3.6.

Significant correlations were found between the English SA-PCS and SA-TSK (p = 0.011), Afrikaans SA-PSC and SA-TSK (p = 0.004) and Xhosa SA-PCS and SA-TSK (p = 0.038); as well as between the Afrikaans SA-PCS and SA-FIQR (p = 0.049) and the Afrikaans SA-TSK and SA-FIQR (p = 0.01).

Table 3.6: Pearson's correlations between various outcome measures

		Pain severity		SA-PCS		SA-TSK		SA-FIQR	
SA-PCS	**N**	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
Afrikaans SA-PCS	26	0.25	0.23	--	--	**0.55**	**0.00†**	**0.39**	**0.04†**
English SA-PCS	22	0.32	0.15	--	--	**0.53**	**0.01†**	0.38	0.08
Xhosa SA-PCS	19	0.30	0.21	--	--	**0.48**	**0.04†**	0.30	0.21
SA-TSK									
Afrikaans SA-TSK	26	0.04	0.84	**0.55**	**0.00†**	--	--	**0.49**	**0.01†**
English SA-TSK	22	0.09	0.66	**0.53**	**0.01†**	--	--	0.51	0.15
Xhosa SA-TSK	19	0.07	0.79	**0.48**	**0.04†**	--	--	0.44	0.06
SA-FIQR									
Afrikaans SA-FIQR	26	0.26	0.20	**0.39**	**0.04†**	**0.49**	**0.01†**	--	--
English SA-FIQR	22	0.32	0.15	0.38	0.08	0.51	0.15	--	--
Xhosa SA-FIQR	19	0.27	0.26	0.30	0.21	0.44	0.06	--	--

†Significance set at p<0.05; SA-PCS =South African Pain catastrophizing scale; SA-TSK = South African Tampa scale for Kinesiophobia; SA-FIQR = South African revised Fibromyalgia Impact Questionnaire; r = Pearson's correlation; p = p-value

PLEASE NOTE:

The final English, Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR can be found in Appendix 5, 6 and 7, respectively.

3.4 Chapter summary

- The aim of this study was to cross-culturally adapt and validate the PCS, TSK and FIQR for use in English-, Afrikaans- and Xhosa-speaking patients with FMS living in the western parts of South Africa, as well as establish the sociodemographic profile of these patients.
- Ninety-three subjects (89 female and 4 male) participated in this study. The mean±SD age was 47.28±10.38 years.
- Of the subjects, 73% were coloured, 41 % were black, 4 % were white and 2% were classified as “other” ethnicity.
- Of the subjects, 44% were Afrikaans-speaking, 35% were English-speaking and 20% were Xhosa-speaking.
- 40.9% of the subjects had a “*lower than grade 12*” education.
- 34.4% of the included subjects were unemployed.
- 36.6% of the subjects were married.
- The mean±SD number of years living with FMS was 5.37±4.88 years.
- The mean±SD pain catastrophizing level among the subjects (n=93) was 36.37±10.40.
- The mean±SD kinesiophobia level among the subjects (n=93) was 50.80±6.52.
- The mean±SD level of impact of fibromyalgia among the subjects (n=93) was 139.61±22.07.
- Modifications to the wording of the items and scoring system were required to ensure that the English, Afrikaans and Xhosa versions of the SA-PCS, SA-TSK and SA-FIQR would be applicable within a South African context.
- The current study findings indicate that the cross-culturally adapted English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR showed good face and content validity, excellent internal consistency, excellent test-retest reliability; as well as satisfactory sensitivity-to-change and cross-sectional convergent validity.
- The SA-PCS, SA-TSK and SA-FIQR can therefore be recommended as simple, efficient, valid and reliable tool which shows satisfactory sensitivity to change, for use among English, Afrikaans and Xhosa-speaking patients with FMS attending the public health sector in the Western Cape area of South Africa.

CHAPTER FOUR

Neurophysiological exploration into the feasibility of a novel VRET exercise program as treatment for pain catastrophization in fibromyalgia patients

4.1 Introduction

Although exercise therapy is advocated as one of the most effective management strategies for fibromyalgia syndrome (FMS) (Haüser et al., 2008; Kelley et al., 2010; Thomas et al., 2010); the implementation of exercise therapy in clinical practice is significantly hampered by poor patient compliance (Busch et al., 2008; Jones et al., 2009; Ablin et al., 2010; Gowans et al., 2010). Strategies to increase compliance to effective treatment modalities such as exercise therapy in FMS are therefore warranted.

The inference that pain catastrophization and subsequent fear-avoidance behaviours may influence the compliance of patients with FMS toward exercise programs, justifies finding treatment approaches to alter pain catastrophization in the management of FMS (van Koulil et al., 2007; Garcia-Campayo et al., 2009). That imagined exposure therapy may effectively reduce pain catastrophizing in patients with FMS (Rodero et al., 2008), makes the investigation of a novel virtual reality exposure therapy (VRET) exercise program as a treatment option for pain catastrophization in FMS, plausible. However, since there is no available VRET exercise program for the treatment of pain catastrophization in patients with FMS; preliminary steps were required prior to the further development and testing of such a program. Initially, it had to be ascertained if visual exposure to catastrophized exercise activities cognitively triggered functional brain areas associated with pain catastrophization in patients with FMS. The premise was that if visual stimuli of the catastrophized exercise activities cognitively triggered pain catastrophization in previously identified functional brain

areas of patients with FMS (Gracely et al., 2004); a VRET program aimed at exposing patients with FMS to visuals of the feared or catastrophized exercises and neutralizing feelings of catastrophization towards exercise activities, could possibly decrease pain catastrophization and subsequently decrease fear of movement. In turn, compliance towards prescribed exercise programs in clinical practice among patients with FMS may be increased.

The study presented in this chapter therefore primarily aimed to test the novel concept that exposing patients with FMS (who catastrophized pain related to exercise), to healthy exercise activities presented via visuals, elicits neurophysiological changes in functional brain areas associated with pain catastrophization which would in turn provide preliminary support for the further development and testing of a specifically-designed VRET exercise program aimed at reducing pain catastrophization toward exercise therapy in patients with FMS.

The following chapter presents the methods and results of an interlinked three-phase exploratory study which was central in testing this novel concept. A brief overview of the three phases included in this study is provided (figure 4.1):

- Phase one involved the development and validation of the fMRI visual task list and included four developmental steps.
- Phase two involved the exploration of the differences in neural correlates using fMRI, when patients with FMS and healthy controls (age, race, gender and socioeconomically matched) are exposed to various visuals of exercise and passive/relaxing activities. Two study groups were included in this phase of the study: a FMS subject group and a healthy control group. The subjects (not the controls) were retained from the study conducted in chapter three. For this phase of the study, it was hypothesized that the FMS subjects, and not the healthy controls,

would display significant activation in functional areas associated with pain catastrophization when exposed to visuals of exercise activities. Preliminary support would therefore be provided for the development and testing of a VRET exercise program aimed at reducing pain catastrophization towards exercise therapy in patients with FMS.

- Phase three involved the testing of the preliminary efficacy and feasibility of a provisionally-designed VRET exercise program on reducing pain catastrophization (subjectively measured using the SA-PCS; objectively measured using fMRI) in patients with FMS. Two study groups were included in this phase of the study: an intervention group and a control group. The subjects for both study groups were retained from the second phase of this study and were all patients with FMS. For this phase of the study it was hypothesized that a reduction in the number of functional areas significantly activated which are associated with pain catastrophization in the intervention group and not the control group, during exposure to visuals of exercise activities, post-intervention, would indicate preliminary efficacy and feasibility of a provisionally-designed VRET exercise program for pain catastrophization in patients with FMS. Preliminary support would therefore be provided for the further development and testing of a VRET exercise program aimed at reducing pain catastrophization towards exercise therapy in patients with FMS.

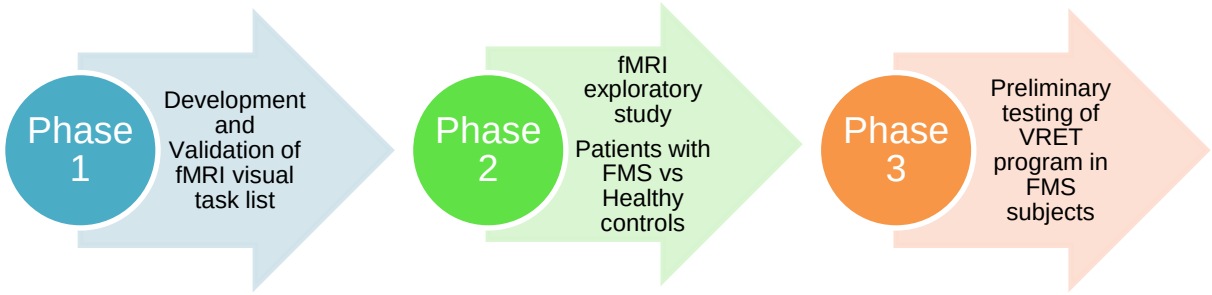


Figure 4.1: The three phases of this study

To simplify matters, the methodological elements (i.e. the objectives, study procedures, etc.) which were not common throughout the three phases, are provided separately for each phase of this study. Methodological elements which were however common between the phases of this study (i.e. ethical considerations, data analysis, etc.) are clearly identified with the following; *applicable to all phases.*

4.2 Methods and Materials

*4.2.1 **Ethical considerations and permissions** (applicable to all phases)*

Ethical approval for this study was obtained from the Health Research Ethics Committee (HREC) of the Stellenbosch University (SU), South Africa during July 2010. The study protocol was also approved by the Committee of Postgraduate Education (CPE), SU, and the Cape Universities Brain Imaging Centre (CUBIC) research committee. Permission to conduct the study at CUBIC was granted by the CUBIC head of department (Appendix 8).

All eligible subjects were required to read and sign an informed consent form (Appendix 4, 9 (focus group study) and 10 (control)) in their preferred language prior to participating in this study. To ensure anonymity, a unique study identification number/code (i.e. VR02-01; VR02-02, etc.) was allocated to each subject on recruitment into this study. Confidentiality of subject information and data was maintained throughout the study, by storing all study data in a locked, access-controlled facility.

*4.2.2 **Overall objectives of this study** (applicable to all phases)*

The overall objectives of this study were to:

1) develop and validate a unique fMRI visual task which would best elicit the construct of interest *viz.* pain catastrophization, in associated functional brain areas of subjects with FMS (and healthy controls) during an fMRI scan;
2) elucidate, using fMRI, the differences in neural correlates which occur between subjects with FMS and healthy controls when these groups are exposed to various visuals of exercise and passive/relaxing activities;
3) ascertain the preliminary efficacy of a provisionally-designed VRET exercise program on pain catastrophization (subjectively and objectively measured) in subjects with FMS, compared to no intervention; and
4) ascertain the feasibility and logistics of using a provisionally-designed VRET exercise program as a treatment for pain catastrophization in subjects with FMS, in terms of:

a) ease of use; b) safety of the intervention/ occurrence of any adverse effects; c) participant acceptability; and d) duration of individual sessions and intervention as a whole.

4.2.3 PHASE ONE: DEVELOPMENT AND VALIDATION OF fMRI VISUAL TASK

The development and validation of the fMRI visual task which would be used during the fMRI scans (phase two and three) was an important part of this study and required meticulous planning. A number of steps were therefore followed to ensure that the final fMRI visual task developed would incorporate the most appropriate visual stimuli to best elicit the construct of interest *viz.* pain catastrophization, in the functional brain areas of subjects with FMS and healthy controls during the fMRI scanning. The four developmental steps for this phase of the study were as follows (figure 4.2):

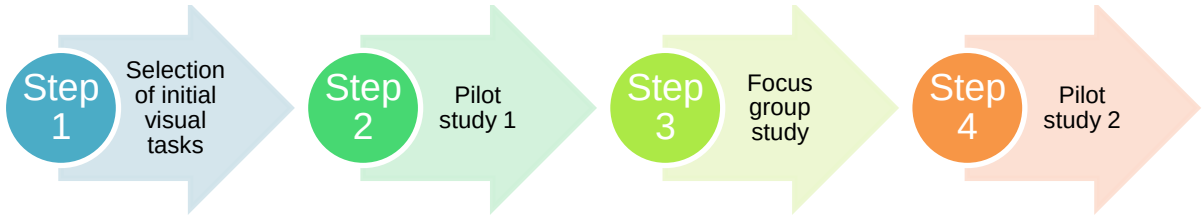


Figure 4.2: Steps 1 to 4 of phase one of this study

This phase of the study was conducted between June 2011 and December 2011. The pilot studies were conducted at CUBIC and the focus group study was conducted at the Tygerberg Hospital's (TBH) Occupational Therapy department. CUBIC is situated at the Stellenbosch University's Tygerberg medical campus, Tygerberg, South Africa. CUBIC is a joint initiative between Siemens, the Stellenbosch University (SU), the University of Cape Town (UCT), and the Medical Research Council (MRC). The core focus of the facility is collaborative neuro-imaging research and boasts Africa's first 3 Tesla (3T) Siemens Allegra MRI scanner. Advanced neuro-imaging of this kind promotes research in a variety of

disciplines, including radiology, psychiatry, psychology, neuroscience, physics and biomedical engineering (http://www.sun.ac.za/cubic).

4.2.3.1 Objective of phase one

The primary objective of this phase of the study was to develop and validate a unique fMRI visual task which would best elicit the construct of interest *viz.* pain catastrophization, in associated functional brain areas of subjects with FMS and healthy controls during an fMRI scan.

4.2.3.2 Study designs utilized during phase one

This phase of the study consisted of two pilot studies and one focus group study. An exploratory, observational within-subject study design was used for the pilot studies. A simple survey-based study design was used for the focus group study.

4.2.3.3 Recruitment of subjects

Eligible subjects were consecutively recruited into this phase of the study. The sample of subjects for this phase of the study was drawn from the subjects with FMS recruited during the validation study (chapter three), based on the following study eligibility:

Study eligibility for pilot study subjects:

- Female adults aged 18 years and older;
- clinically diagnosed with FMS according to the American College Rheumatology (ACR) criteria by a qualified rheumatologist;
- registered at the TBH Rheumatology clinic;
- South African citizens residing in and around the Cape Metropole area;
- spoke, comprehended and were proficient in either the English, Afrikaans or Xhosa language;

- scored more than 24 points on the SA-PCS and more than 37 points on the SA-TSK;
- were willing to undergo fMRI scanning.

Subjects were excluded from the pilot studies if they:

- were diagnosed with any other conditions not related to FMS i.e. cancer; HIV/AIDS
- had severe physical disabilities;
- suffered from other chronic rheumatoid conditions i.e. Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), etc.;
- suffered from psychological/psychiatric disorders i.e. bipolar disorder, etc.;
- had previously been hospitalized for a major psychiatric disorder;
- had an uncontrolled endocrine or allergic disorder;
- were using medication other than the prescribed pharmacologic agents for FMS symptoms;
- were currently or had previously abused any illicit substances or alcohol;
- displayed any contraindications which prohibited the use of fMRI, i.e. cardiac pacemakers, metal implants, claustrophobia, pregnancy and cochlear implants, etc.;
- had a bust and chest size of more than 1.5m in circumference since the MRI scanner at CUBIC does not cater for bust and chest sizes larger than 1.5m in circumference;
- were unable to discontinue intake of anti-depressants four weeks prior to commencement of study;
- were not fully comprehensive of what the project entailed and what was expected of them.

Study eligibility for the focus group subjects:

- Female adults aged 18 years and older;
- clinically diagnosed with FMS according to the ACR criteria by a qualified rheumatologist;

- registered at the TBH Rheumatology clinic;
- South African citizens residing in and around the Cape Metropole area;
- spoke, comprehended and were proficient in either the English, Afrikaans or Xhosa language.

Subjects were excluded from the focus group study if they:

- had severe physical disabilities;
- suffered from other chronic rheumatoid conditions i.e. SLE, RA, etc;
- were currently or had previously abused any illicit substances or alcohol;
- were not fully comprehensive of what the project entailed and what was expected of them.

4.2.3.4 Study instruments and outcome measurement tools

The following outcome measurement tools were used during phase one:

- Sociodemographic form (Appendix 1)
- Pain severity scale (available on the sociodemographic form-Appendix 1)
- *South African Pain catastrophizing scale (SA-PCS):* A self-report measure, the PCS is a broad measure of pain catastrophization and consists of 13 items scored using a 5-point Likert scale. The cross-culturally adapted English, Afrikaans and Xhosa SA-PCS showed good face and content validity, excellent internal consistency (with Cronbach's α = 0.981, 0.984 and 0.970 for the English, Afrikaans and Xhosa SA-PCS, respectively), excellent test-retest reliability (with ICC's of 0.904, 0.908 and 0.891 for the English, Afrikaans and Xhosa SA-PCS, respectively); as well as satisfactory sensitivity-to-change (with a minimum detectable change (MDC) of 8.84, 9.03 and 9.25 for the English, Afrikaans and Xhosa SA-PCS, respectively) and cross-sectional convergent validity (when compared to pain severity, as well as the South African versions of the TSK and FIQR) (chapter three). (Appendix 5)

- *South African Tampa scale for Kinesiophobia (SA-TSK):* The TSK is a self-report instrument designed to assess fear of pain and activity. It consists of 17 items each rated on a 4-point Likert scale. The cross-culturally adapted English, Afrikaans and Xhosa SA-TSK showed good face and content validity, excellent internal consistency (with Cronbach's α = 0.940, 0.961 and 0.965 for the English, Afrikaans and Xhosa SA-TSK, respectively), excellent test-retest reliability (with ICC's of 0.82, 0.81 and 0.83 for the English, Afrikaans and Xhosa SA-TSK, respectively); as well as satisfactory sensitivity-to-change (with a MDC of 7.76, 7.89 and 7.04 for the English, Afrikaans and Xhosa SA-TSK, respectively) and cross-sectional convergent validity (when compared to pain severity as well as South African versions of the PCS and the FIQR) (chapter three) (Appendix 6).
- *South African Revised Fibromyalgia Impact Questionnaire (SA-FIQR):* The FIQR is an updated and shortened version of the FIQ that has good psychometric properties, can be completed in less than 2 minutes and is easy to score. The cross-culturally adapted English, Afrikaans and Xhosa SA-FIQR showed good face and content validity, excellent internal consistency (with Cronbach's α = 0.946, 0.941 and 0.932 for the English, Afrikaans and Xhosa SA-PCS, respectively), excellent test-retest reliability (with ICC's of 0.88, 0.87 and 0.85 for the English, Afrikaans and Xhosa SA-FIQR, respectively); as well as satisfactory sensitivity-to-change (with a MDC of 21.15, 21.76 and 21.59 for the English, Afrikaans and Xhosa SA-PCS, respectively) and cross-sectional convergent validity (when compared to pain severity as well as South African versions of the PCS and TSK) (chapter three). (Appendix 7)
- *GPPAQ* (Appendix 2) (see section 3.2.7.6 in chapter 3)
- *Neurophysiological observation using fMRI:* A Siemens MAGNETOM Allegra 3T MRI scanner was used for the fMRI scanning procedures. The Allegra is a dedicated brain scanner and currently the most advanced brain imaging instrument on the

market. The Siemens MAGNETOM Allegra 3T MRI scanner and the fMRI scanning room situated at CUBIC are depicted in figure 4.3.

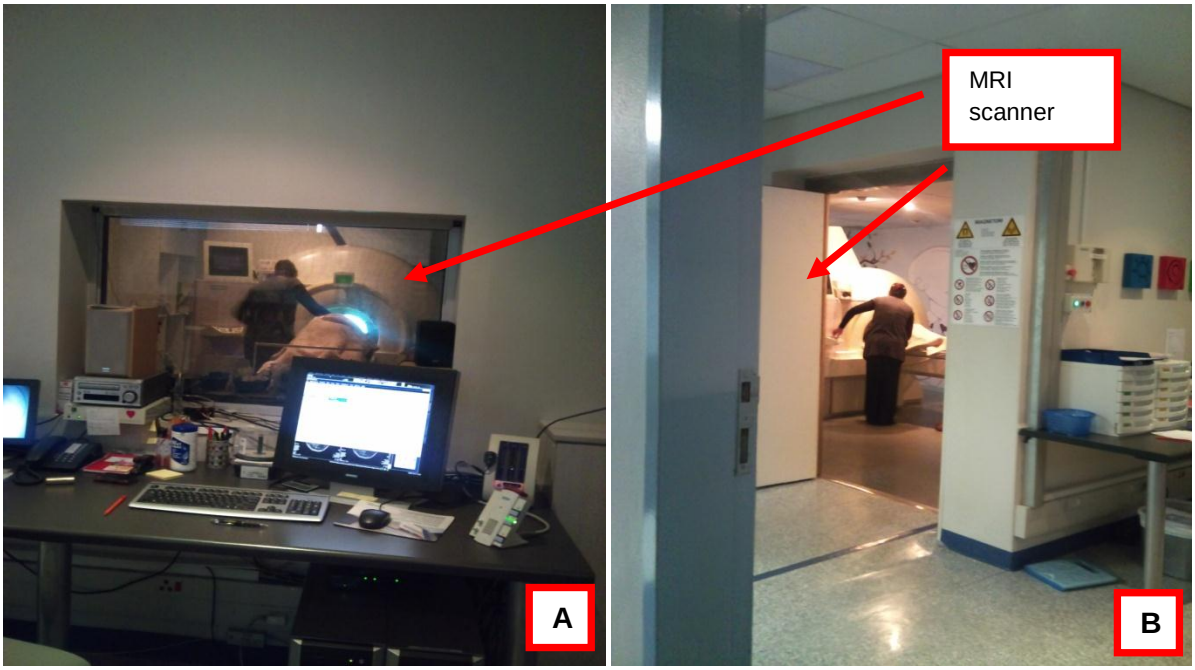


Figure 4.3: (A and B): The Siemens MAGNETOM Allegra 3 Tesla MRI scanner and the fMRI scanning room at CUBIC

4.2.3.5 Study Procedures: The four developmental steps of phase one

4.2.3.5.1 Step 1: Selection of initial visual tasks

For the fMRI visual task, visuals depicting exercise activities (active visuals) and passive/ relaxing activities (passive visuals) were required. Using the results generated from the modified PHODA survey in the validation study (chapter three; section 3.3.2.4), a provisional set of active visuals for the fMRI task was compiled. The visuals most frequently reported as catastrophized or feared were selected. Active visuals consisted of exercise activities i.e. cycling, leg-lifts, aerobics, running, stretching, treadmill walking, sit-ups and tennis. Passive visuals were selected based on the principal researcher's own prerogative, and in consultation with the supervisors. Passive visuals consisted of passive/relaxing activities i.e. walking/sitting on the beach, drinking tea, reading a book, taking a bubble bath, etc.

Initially, the visuals chosen for the first pilot study were formatted and chosen based on the following reasons:

- Visuals were converted from colour images to black and white. Initially it was thought that too much colour in the visuals would distract the subject from what was being depicted in the image and therefore subjects would not concentrate on the activity being shown.
- Based on the results of the profile study conducted as part of the validation study (chapter three), it was found that 22.06% of the subjects were divorced or separated and 13% were widowed. Furthermore, the rate of domestic violence against women in South Africa is exceptionally high (Rashe., 2008). It was therefore decided that visuals depicting images of couples could probably provoke negative feelings or feelings of depression in some of the subjects. For this reason, no visuals depicting images of couples were included in the fMRI visual task.
- Based on the high level of drug usage among the youth residing in the Western part of South Africa (Nyabadza et al., 2010), as well as the high crime rates (http://www.uact.org.za/statistics), it was assumed that some of the subjects included in this study may have had some or the other drug- or crime-related problem their children (i.e. their children being in jail, or on drugs). It was therefore decided that visuals depicting children could provoke negative feelings or feelings of depression in some of the subjects. For this reason, no visuals depicting children were included in the fMRI visual task.
- Based on the high level of drug and alcohol usage among the adult population residing in the Western part of South Africa (Nyabadza et al., 2010), it was presumed that some of the subjects included in this study may have had some or other drug- or alcohol-related problem (i.e. husbands or themselves abuse/or have abused alcohol or drugs). It was therefore decided that visuals depicting the use of alcohol or drugs could provoke negative feelings or feelings of depression in some of the subjects. For

this reason, no visuals depicting the use of alcohol or drugs were included in the fMRI visual task.

4.2.3.5.2 Step 2: Pilot study 1

Subject preparation

A pilot study was conducted to test the logistics (including duration, applicability and acceptability) of the fMRI visual task and procedure. One subject clinically diagnosed with FMS and meeting the subject inclusion criteria previously stipulated for the main study was included in the pilot study. The subject was however not included in the main studies which followed. The pilot study and fMRI procedures were thoroughly explained to the subject and on agreeing to participate in the pilot study; the subject was requested to read and sign an informed consent form (Appendix 4). The subject was screened using the CUBIC MRI screening form to assess if the subject possessed any conditions contraindicated for fMRI scanning. The subject was then requested to complete a socio-demographic form, the SA-PCS, SA-TSK, SA-FIQR and the GPPAQ. An appointment for an fMRI scan was scheduled on a day and at a time most convenient for the subject.

fMRI scan

On the day of the scheduled pilot neurophysiological analysis (fMRI scanning) appointment, the subject was again informed of the procedure and asked to comply with all the regulations of CUBIC. Any questions raised by the subject regarding the fMRI scanning process and equipment were addressed by the principal researcher. The subject was escorted to the fMRI chamber room and asked to lie down inside the fMRI chamber. Foam cushions were used to immobilize the subject's head. The subject was required to wear MRI compatible earplugs (to minimize scanner noise) and earmuffs (for communication with the radiographer/principal researcher during the scanning process).

A simple block design was used for the fMRI task which allowed for simple modeling of the blood oxygenation level dependent (BOLD) response, resulting in more robust and reproducible results (Friston et al., 1999 cited in Amaro et al., 2006). The fMRI visual task was designed using the E-Studio 2.0.8.90 (E-Prime 2.0) software available at the CUBIC facility. The fMRI visual task entailed the application of the following two stimuli:

- *Active visuals (30 s clips of various visuals of exercise/physical activities i.e. cycling, running, etc.);*
- *Passive visuals (30 s clips of visuals of everyday sedentary/relaxing activities i.e. reading a book/magazine, drinking tea, etc.).*

Initially, the fMRI task was set up to include 12 x 30 s 'off'/rest periods (no stimulus) and 12 x 30 s 'on' periods (stimuli). The 'off'/rest period comprised of a fixation visual (a small grey block in the middle of a black screen). The total duration of the task was 720 s (12 minutes). The 30 s 'on' periods consisted of either 6 x active visuals (active condition) or 6 x passive visuals (passive condition). Each visual was flashed for 5 s. The active visuals, passive visuals and rest period were alternated. The design of the fMRI task model was as follows, where A = active condition, B = passive condition and r = rest period:

rArBrArBrArBrArBrArBrArB

In total, from preparation to completion, the scanning procedure for each subject lasted approximately 42 minutes (15 minutes preparation + 9 minutes MEMPRAGE (structural) scan + 12 minutes fMRI task ± 5 minutes extra).

Figure 4.4 depicts the timing model of the fMRI task used during pilot study one:

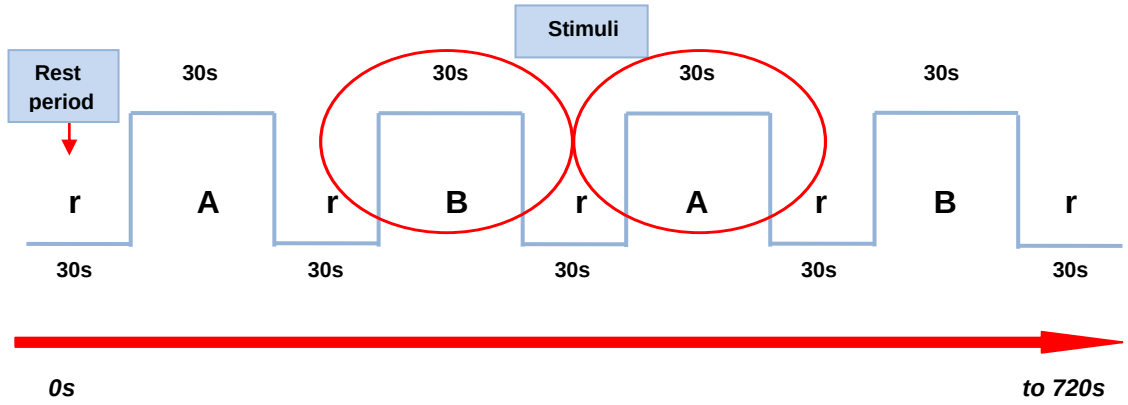


Figure 4.4: The fMRI task model for pilot study 1 (block design)

Post-fMRI scanning

Following the fMRI scan, the pilot subject was requested to comment on the instructions given, the individual visual tasks, the clarity and ease of interpreting the visual tasks, the duration of the tasks, and the duration of the entire fMRI scan. Please note, that the comments/suggestions requested from the subject were however not formally collected in a standard qualitative format, but rather in an informal manner. All comments and suggestions provided by the subject were documented and addressed; and the fMRI task was revised accordingly.

4.2.3.5.3 Step 3: Focus group study

Subject preparation

Following the first pilot study, a focus group study was conducted amongst a group of subjects with FMS meeting the previously stipulated study eligibility criteria to further validate the fMRI visual task. A group of English, Afrikaans and Xhosa-speaking patients with FMS were invited to participate in the focus group study. The aim of the focus group study was to ascertain the emotions provoked by the visual stimuli intended for the fMRI visual task, and whether the visuals provoked any negative connotations (other than pain catastrophization or fear), or were associated with negative personal events such as a divorce or a death in

the family. The study procedure was thoroughly explained to the subjects in their preferred language, and on agreeing to participate, subjects were requested to read and sign an informed consent form (Appendix 9). All the subjects were asked to meet at the TBH Occupational Therapy department on a specific date.

Focus group session

At the beginning of the focus group session, a form specially designed by the principal researcher was handed to the subjects. The form consisted of a list of numbers corresponding with the order in which the visuals would be presented to the group. The visuals were presented to the group on a laptop using a MS PowerPoint presentation. Tick boxes denoting a range of "emotions/feelings" were placed adjacent to the corresponding numbers (Appendix 11). The "emotions/feelings" were as follows: *"happy thoughts", "feel relaxed", "feel/think nothing", 'think of pain" and "feel sad/depressed"*. Adequate space next to the corresponding numbers was also provided on the form for subjects to write down what they thought was being represented in the visual i.e. what activity was being represented, and if they associated the visual with any personal experience. No other information i.e. subject's name, personal information, etc. was requested from subject on the form. Subjects were instructed to carefully look at each visual presented to them and to tick the box next to the corresponding number on the form which best represented what they "felt" or "thought" when looking at that particular visual. To ensure subjects completely comprehended what was expected of them, the principal researcher demonstrated a simple example. Prior to presenting the visuals, all subjects were asked if they understood and were instructed to ask for assistance at any time. Subjects who had difficulty in writing were assisted by the principal researcher, research assistant or translator. The information collected during the focus group session was extracted and collated. Visuals which were reported to provoke/elicit other negative emotions besides pain catastrophization or were reported to be associated with negative or personal events, were discarded.

4.3.2.5.4 Step 4: Finalization of fMRI visual task

Information regarding the visual tasks retrieved from the first pilot study and focus group study were carefully examined and all suggestions and comments provided were addressed. Changes to the provisionally-designed fMRI visual task and procedure were made accordingly and re-piloted using the same pilot subject used in first pilot study. The pilot subject again underwent an fMRI scanning procedure during which the subject was exposed to active and passive visual stimuli. The procedure was identical to the procedure described for the first pilot study, except that duration of the fMRI was reduced from 720 s to 600 s. Final comments and suggestions provided by the subject were documented and final changes were made to the fMRI visual task list. In addition, the fMRI data acquired for the pilot subject during the second pilot study were analyzed accordingly, to assess if the processing of the data and the output of the data were accurate.

The tasks, instructions, time duration and procedure for the fMRI task were finalized as follows:

The final MRI visual task entailed the application of the following two stimuli:

1) *Active visuals (30 s clips of various visuals of exercise/physical activities)*
2) *Passive visuals (30 s clips of visuals of everyday sedentary/relaxing activities)*

The task was set up to include 12 x 20 s ‘off’/rest periods (no stimulus) and 12 x 30 s ‘on’ periods (stimuli). The total duration of the task was 600 s (10 minutes). The duration of the rest period was reduced from 30 s to 20 s. The ‘on’ periods consisted of either 6 x active visuals, or 6 x passive visuals. Each visual was flashed for 5 s within the 30 s period allocated for that particular condition. The ‘off’/rest period comprised of fixation visual (a small grey block in the middle of a black screen). The design of the fMRI task model was as follows where A = active condition, B = passive condition and r = rest period:

rArBrArBrArBrArBrArBrArB

In total, from preparation to completion, the scanning procedure for each subject lasted approximately 40 minutes (15 minutes preparation + 9 minutes MEMPRAGE (structural) scan + 10 minutes fMRI task ± 5 minutes extra).

Figure 4.5 depicts the timing model of the fMRI task used during pilot study two:

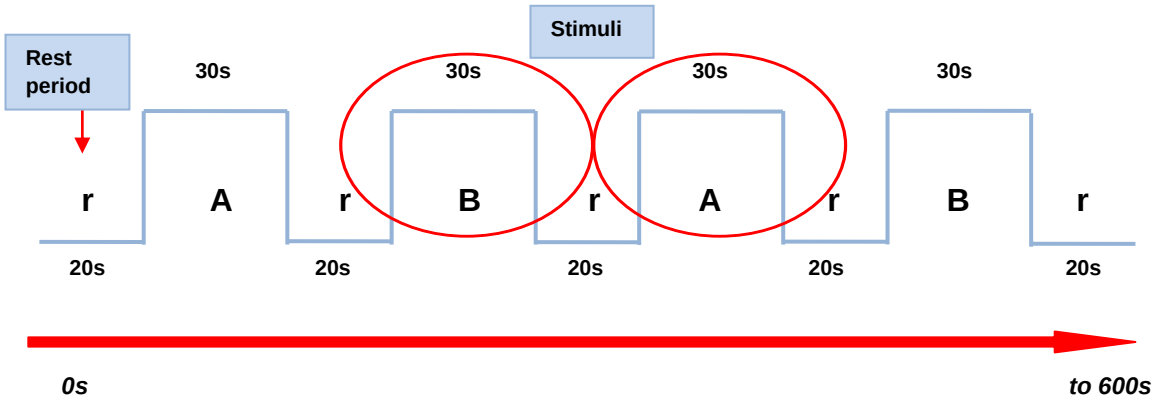


Figure 4.5: The fMRI task model for pilot study 2 (block design)

The final fMRI visual task and procedure described above was applied in phase two and three of this study.

4.2.4 PHASE TWO: fMRI EXPLORATORY STUDY

This phase of the study was conducted at CUBIC between February 2012 and April 2012.

4.2.4.1 Objective of phase two

The primary objective of this phase was to elucidate, using fMRI, the differences in neural correlates which occur between subjects with FMS and healthy controls when these groups are exposed to various visuals of exercise and passive/relaxing activities.

4.2.4.2 Study design used for phase two

An exploratory, observational within-subject/between-group study design was used for this phase of the study.

4.2.4.3 Recruitment of FMS subjects and matched controls

Two study groups were included in this phase of the study: a FMS subject group and a healthy control group. Eligible FMS subjects and matched healthy controls were consecutively recruited into the study. The sample of subjects for this study was drawn from the FMS subjects recruited during the validation study (chapter three), based on study eligibility. Controls were purposefully-selected and matched to each FMS subject based on age, race, gender and socio-economical status. Matched controls were recruited from areas surrounding the TBH area since access to and from the study setting were deemed easier. The following study eligibility criteria applied.

FMS subjects were included in this study if they:

- were female adults aged 18 years and older;
- had been clinically diagnosed with FMS according to the ACR criteria by a qualified rheumatologist;
- were registered at the TBH Rheumatology clinic;

- were South African citizens residing in and around the Cape Metropole area;
- had previously participated in the validation study (chapter three)
- spoke, comprehended and were proficient in either the English, Afrikaans or Xhosa language;
- scored more than 24 points on the PCS and more than 37 points on the TSK
- were willing to undergo two fMRI scans (one at baseline and one post-intervention)
- were willing to participate in the intervention study.

FMS subjects were excluded from this study if they:

- were diagnosed with any other conditions not related to FMS i.e. cancer; HIV/AIDS
- had severe physical disabilities;
- suffered from chronic rheumatoid conditions i.e. SLE, RA, etc;
- suffered from psychological/psychiatric disorders i.e. bipolar disorder, etc;
- had previously been hospitalized for a major psychiatric disorder;
- had an uncontrolled endocrine or allergic disorder;
- were using medication other than the prescribed pharmacologic agents for FMS symptoms;
- were currently or had previously abused any illicit substances or alcohol;
- had been diagnosed with epilepsy, or other conditions contraindicated in the use of visual exposures to stimuli or virtual reality;
- displayed any contraindications which prohibited the use of fMRI, i.e. cardiac pacemakers, metal implants, claustrophobia, pregnancy and cochlear implants, etc.;
- had a bust and chest size of more than 1.5m in circumference since the MRI scanner at CUBIC does not cater for bust and chest sizes larger than 1.5m in circumference;
- were unable to discontinue intake of anti-depressants 4 weeks prior to commencement of study;

- were not fully comprehensive of what the project entailed and what was expected of them.

Matched controls were included in this study if they:

- were healthy, female adults aged 18 years and older;
- were South African citizens residing in and around the Cape Metropole area;
- spoke, comprehended and were proficient in either the English, Afrikaans or Xhosa language;
- were willing to undergo fMRI scanning.

Matched controls were excluded from this study if they:

- were suffering from conditions like FMS, cancer, SLE, RA etc,
- had severe physical disabilities;
- suffered from psychological/psychiatric disorders i.e. bipolar disorder, etc;
- had previously been hospitalized for a major psychiatric disorder;
- were currently or who had previously abused any illicit substances or alcohol;
- displayed any contraindications which prohibited the use of fMRI, i.e. cardiac pacemakers, metal implants, claustrophobia, pregnancy and cochlear implants, etc.;
- had a bust and chest size of more than 1.5m in circumference since the MRI scanner at CUBIC does not cater for bust and chest sizes larger than 1.5m in circumference;
- were not fully comprehensive of what the project entailed and what was expected of them.

4.2.4.4 Sample size

Given that the effect of a VRET program for pain catastrophization in patients with FMS has not been previously investigated, and the sample size for this project was heavily dependent on the available project funding, the number of subjects included in this study was limited

considerably. The total number of subjects for this phase of study was 22 (13 FMS subjects and nine matched controls).

4.2.4.5 Study instruments/outcome measurement tools used during phase two

The following study instruments and outcome measurement tools were used during phase two of this study:

- Sociodemographic form (Appendix 1)
- GPPAQ (Appendix 2)
- SA-PCS (Appendix 5)
- SA-TSK (Appendix 6)
- SA-FIQR (Appendix 7)
- Neurophysiological observation using fMRI

*Please note that not all of the outcome measurement tools were administered to both the FMS subject group and healthy control group as some of the outcome measurement tools were not deemed relevant for the healthy control group in this phase of the study, and some of the forms/outcome measures had been completed by the FMS subject group during the validation study (chapter three). The sociodemographic forms and GPPAQ were administered to the healthy control group only, since the FMS subjects had already completed these forms during the validation study (chapter three). Information regarding the sociodemographics and physical activity levels of the FMS subjects was therefore retained from the results of the validation study (chapter three). In addition, SA-PCS, SA-TSK, SA-FIQR scores were also retained for the FMS subject group from the results of the validation study (chapter three). fMRI was however administered to both groups.

4.2.4.6 Study procedure of phase 2

Once the fMRI visual task list was finalized (phase 1; step 4), the main fMRI exploratory study commenced. Eligible subjects were screened using the CUBIC MRI screening form to assess if the subjects possessed any contraindications for fMRI scanning. Study procedures were thoroughly explained to each subject as they were recruited into this study and a neurophysiological (fMRI) analysis appointment was scheduled for a day and time most convenient for the subjects. Remuneration for transport was provided to subjects to and from the CUBIC facility on the day of their scheduled appointment.

On the day of the scheduled neurophysiological analysis, subjects were again informed of the procedure and asked to comply with all the regulations of CUBIC. Any questions raised by the subjects regarding the neurophysiological analysis process and equipment were addressed by the principal researcher. Subjects were escorted to the MRI chamber room situated in the CUBIC and asked to lie down inside the MRI chamber. Foam cushions were used to immobilize the head. The subjects were required to wear MRI compatible earmuffs and earplugs for communication with the principal researcher/radiographer and to minimize scanner noise.

- ***fMRI task***

The fMRI task finalized at the end of the phase one of this study was applied during this phase of the study. To reiterate, however, a simple block design was used for the fMRI task and the fMRI task entailed the application of the following two stimuli:

1) *Active visuals (30 s clips of various visuals of exercise/physical activities);*
2) *Passive visuals (30 s clips of visuals of everyday sedentary/relaxing activities).*

The task was set up to include 12 x 20 s ‘off’/rest periods (no stimulus) and 12 x 30 s ‘on’ periods (stimuli). The total duration of the task was 600 s (10 minutes). The ‘on’ periods

consisted of either 6 x active visuals, or 6 x passive visuals. Each visual was flashed for 5 s within the 30 s period allocated for that particular condition. The 'off'/rest period comprised of a fixation visual (a small grey block in the middle of a black screen). In total, from preparation to completion, the scanning procedure for each subject lasted approximately 40 minutes (15 minutes preparation + 9 minutes MEMPRAGE (structural) scan + 10 minutes fMRI task ± 5 minutes extra).

4.2.5 PHASE THREE: PRELIMINARY TESTING FOR THE EFFICACY OF A NOVEL VRET EXERCISE PROGRAM

This phase of the study was conducted between April 2012 and July 2012.

4.2.5.1 Objectives of phase three

The primary objectives of this phase of the study were to:

1) ascertain the preliminary efficacy of a provisionally-designed VRET exercise program on pain catastrophization (subjectively and objectively measured) in FMS subjects, compared to no intervention; and
2) ascertain the feasibility and logistics of using a provisionally-designed VRET exercise program as a treatment for pain catastrophization in FMS subjects, in terms of: a) ease of use; b) safety of the intervention/ occurrence of any adverse effects; c) participant acceptability; and d) duration of the individual sessions and entire intervention.

4.2.5.2 Study settings for phase three

The treatment rooms in the Physiotherapy and Motion analysis clinic (Body in Motion) situated on the first floor of the teaching block of the SU's Tygerberg medical campus, as well as the CUBIC facility were used as the settings for this study.

4.2.5.3 Study design of phase three

A quasi, within-subject/between groups experimental (pre- and post-, with/without treatment) study design was used for this phase of the study.

4.2.5.4 Recruitment of subjects

Subjects for this phase of the study were retained from phase three (FMS subject group).

4.2.5.5 Study instruments/outcome measurement tools used during phase three

The following study instruments and outcome measurement tools were used during phase three of this study:

- SA-PCS (Appendix 5)
- SA-TSK (Appendix 6)
- Neurophysiological observation using fMRI

4.2.5.6 Study Procedure for phase three

The study procedure was once again thoroughly explained to each subject and the subjects were reminded that they may withdraw from the study if they wish to do so.

4.2.5.6.1 Intervention

- *Hardware*

Visual exposure to exercise activities were delivered via a virtual reality head-mount display (VR HMD); namely the eMagin Z800 3DVISOR linked to an ASUS K61IC series laptop. The eMagin Z800 3DVISOR has a highly sophisticated built-in head tracker which allows the user six degrees of freedom in motion. The HMD is placed on the head of the user, blocking off the surrounding environment. The visuals played to the HMD via a connected laptop are viewed on two 3D OLED 0.59 inch micro displays, which to the user seem to play as huge

as a 105- inch screen. These specific features of the eMagin Z800 3DVISOR enhance the immersion of the user into the virtual environment (www.emagin.com).

Figure 4.6 illustrates the eMagin Z800 3DVISOR being worn by a subject during the VRET exercise program.

***Figure 4.6: The* eMagin Z800 3DVISOR (B) being worn by a subject during the VRET program sessions (A). (Reproduced with permission: www.emagin.com)**

- *Software*

The provisionally-designed VRET exercise program was compiled, partly by using the results of the modified PHODA (chapter three) and partly by using previous literature regarding the most appropriate exercises for patients with FMS (Kelley et al., 2010; Thomas et al., 2010). The exercise component of the VRET exercise program was designed using PERFECT FIT®, which is a new online-mobile exercise solution designed to help guide patients on their journey to getting fit and staying fit. What is unique about PERFECT FIT® is that health professionals (i.e. physicians, physiotherapists, etc) across the globe can use the program to set up tailor-made exercise programs for patients. Health professionals can register online and have access to over 2000 exercise animations and 500 workouts and exercises programs can easily be created, modified, saved and printed - and can also be shared with patients via Facebook, Twitter, LinkedIn and email (http://www.perfectfitfree.com).

- *The VRET exercise program*

Based on previous literature pertaining to the basics of cognitive-behavioural therapy (CBT) (Wright et al., 2006), and using the PERFECT FIT® software, a provisionally-designed VRET exercise program was developed. The VRET exercise program consisted of the following components:

1) Introductory presentation, introducing the subjects to the program and the equipment.
2) Brief presentation informing the subjects of the benefits of exercises for FMS (based on previous literature) (Kelley et al., 2010; Thomas et al., 2010).
3) Verbal exercises – Subjects were requested to repeat the following out loud at the end of the presentation:

   I am in control. Fibromyalgia does not control me.

   I can do exercises.

   Exercises will not harm me.

Exercises will not worsen my condition.

Exercises are good for me.

Exercises will reduce my pain and symptoms.

Exercises will improve my quality of life.

4) Homework – A copy of the verbal exercises was given to each subject, along with a copy of the entire MS PowerPoint presentation. The subjects were required to go home and place the copy of the verbal exercise on their bathroom mirror or some place in their home where they would see the copy every day. The subjects were further requested to repeat the verbal exercise everyday and every time they passed the copy on the mirror/wall.

5) VRET component – A list of 40 exercise activity animations were compiled using PERFECT FIT® (http://www.perfectfitfree.com). Each exercise animation was set to run for approximately 30 to 40 seconds. The exercises were not programmed to run in any particular order, and were therefore not progressive in anyway. Subjects were however exposed to progressively more exercise animations at each session, starting with exposure to 15 exercise animations during the second session, and progressing to 40 exercise animations at the final session (session 6). The duration of exposure to exercise activities was progressively increased at each session, starting with 10 minutes during the first session to approximately 30 minutes at the final session (session 6).

The individual sessions of the provisionally-designed VRET exercise program were as follows (Table 4.1):

Table 4.3: Outline of VRET exercise program

Week	Session	VRET exercise 3 week program	Total duration of session	Duration of VRET component
1	1	• Welcome • Introduction • Brief presentation on the benefits of exercises for FMS • Verbal exercise • Homework	45 mins	0 mins
	2	• Reiteration of benefits of exercises for FMS • Assessment of homework • VRET: Exposure to 15 exercise animations • Verbal exercise • Homework	45 mins	10 mins
2	3	• Reiteration of benefits of exercises for FMS • Exposure to 20 exercise animations • Verbal exercise • Homework	30 mins	15 mins
	4	• Reiteration of benefits of exercises for FMS • Exposure to 30 exercise animations • Verbal exercise • Homework	30 mins	20 mins
3	5	• Reiteration of benefits of exercises for FMS • Exposure to 35 exercise animations • Verbal exercise • Homework	30 mins	25 mins
	6	• Reiteration of benefits of exercises for FMS • Exposure to 40 exercise animations • Verbal exercise • Take home message • Homework	45 mins	30 mins

In figure 4.7, screenshots of a few of the exercise animations incorporated into the VRET exercise program are depicted.

Figure 4.7: Screenshots (A-F) of some of the exercises incorporated into the VRET exercise program (Source: PERFECT FIT® available at http://www.perfectfitfree.com***)***

4.2.5.6.2 Description of study groups

- *VRET group (intervention)*

The provisionally-designed VRET exercise program was conducted over a three-week period. Subjects were asked to attend twice weekly 30- to 45-minute sessions for three weeks (total six sessions). The duration and frequency of the entire intervention (twice weekly for three weeks) was based on our anticipation that too long of a period between the baseline and post-intervention fMRI scan could have introduced unwanted biases. During the sessions, subjects were asked to wear the VR HMD and follow the instructions viewed through the OLED micro displays.

- *'Waiting list' group (control)*

The control condition consisted of a 'waiting list' group. Subjects assigned to the waiting list received no treatments, no education about the effects/benefits of exercising on FMS and no behavioural techniques during the three-week study period. The subjects were instructed to continue with their normal activities and to return to the study venue at the end of the three-week study period.

4.2.5.6.3 Procedure of sessions (intervention group)

The original sociodemographic information, GPPAQ, SA-PCS, SA-TSK and SA-FIQR scores obtained during the validation study (chapter three), as well as fMRI data obtained in phase two, were retained as subject baseline data for this phase of the study. During the treatment sessions, subjects allocated to the intervention group were placed in an isolated room. The provisionally-designed VRET exercise program described in section 4.2.5.6.1, was administered via the VR HMD. The principal researcher conducted all the VRET sessions, with the help of the research assistant. The SA-PCS and SA-TSK was administered at beginning of the treatment program and at the end the program (after three weeks).

Information relating to the feasibility and logistics of the study was collected from the intervention group at the end of the three-week study period.

Appointments to return to CUBIC after three weeks were scheduled for the intervention group and the control group subjects when both groups underwent a second fMRI analysis (post-intervention). Post-intervention fMRI data were compared to baseline fMRI data acquired during phase two of this study. The same procedure described in section 4.2.4.6 for fMRI data acquisition was followed.

4.2.5.6.4 Logistical information and potential feasibility

A post-treatment survey form was used to collect information pertaining to the following (Appendix 12): a) ease of use; b) safety of the intervention/ occurrence of any adverse effects; c) participant acceptability; and d) duration of the individual sessions and entire intervention.

**Please note: The following methodological procedures apply to all phases of this study.*

4.2.6 Loss to follow-up

Where subjects later refused or were unable to participate in this study, data for that particular subject was retained regardless as to how many sessions were attended, etc. and analyzed accordingly. All reasons for termination or suspension of treatments were documented.

4.2.7 Data collection and storage

Neurophysiological changes occurring during the fMRI procedure were recorded. Standard MPRAGE (MEMPR - structural brain scans) and blood oxygenation level dependent (BOLD) sequences were acquired. fMRI data for each subject was saved and stored on the CUBIC

facility's server, on a CD and on an external hard-drive, under the reference number allocated to that subject at the beginning of this study. Back-up files of all data were made in the event of data being lost and were stored in a separate location. A research assistant administered and collected all SA-PCS and SA-TSK questionnaires from subjects. Data collected were stored in subject's respective folders. Folders, data and back-up data were stored in a locked room at all times. All subject identification and information were kept confidential throughout the study.

4.2.8 Statistical analysis

4.2.8.1 Functional imaging

BOLD contrasts were collected for each participating subject using a Siemens MAGNETOM Allegra 3 Tesla (3T) MRI scanner (Siemens, Munich, Germany). T1-weighted structural images were acquired interleaved in a sagittal direction and a isocenter position, using a multi-echo MPRAGE (MEMPR) sequence (van der Kouwe et al., 2008) with the following parameters: echo time (TE) 1.53 ms; recovery time (TR) 2.53 ms; flip angle 7°; 256 3 256 pixel matrix; field of vision (FOV) 256 mm; 1.3 x 1 x 1.3 mm voxels; 128 partitions per slab. This structural scanning session was followed by two functional scan sessions using multi-slice, echoplanar imaging fMRI acquisition with the following parameters: TE 23 ms;

TR 1.6 s; flip angle 73°; 64 3 64 pixel matrix; FOV 255 m; 30 horizontal 3 mm slices. These parameters allowed coverage of the entire brain with 4 mm^3 voxels within 5 s. During each fMRI session, the first four scans were discarded to allow for saturation of the tissue. Starting on the fourth scan, 20 s resting periods ('off' condition) were alternated with 30 s stimuli ('on' condition/active or passive visuals) (section 4.2.4.6). The analysis was performed on the scans acquired during the 'on' and `off' conditions.

4.2.8.1 Contrasts/Conditions

BOLD contrasts were acquired during the fMRI scans for the subject during the following conditions: 1) *active>rest* condition (where brain activations during the rest period were subtracted from the active condition); 2) *passive>rest* condition (where the brain activations during the rest period were subtracted from the passive condition); 3) *active>passive* condition (where the brain activations during the passive condition were subtracted from the active condition); and 4) *passive>active* condition (where the brain activations during the active condition were subtracted from the passive condition). The condition of interest was however the *active>passive condition* since it was expected that significant activations of specific functional brain areas during this condition would signify association with pain catastrophization (the construct of interest) the most.

4.2.8.2 Pre-processing of data

Data acquired from the subjects were pre-processed by the principal researcher using Oxford's FMRIB Software Library (FSL), which is currently available at CUBIC. The principal researcher was trained in using FSL by Dr B. Spottiswoode (previous head of CUBIC). FSL is a collection of functional and structural brain imaging analysis tools, written by members of the Image Analysis Group at the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University. FSL is distributed as freeware and most of the tools can be run both from the unix command line and as a graphical user interface (GUI) (Smith et al., 2004). FSL standard routines and templates were used for pre-processing of functional MRI data: Re-alignment, Normalization (resulting voxel size 2×2×2 mm), and Smoothing (8 mm isotropic Gaussian kernel; high-pass filter cut-off to 100 s). Each session of image acquisition was defined as a separate session in the re-alignment procedure. Head motion was determined by motion detection software and visual inspection of raw and processed images. Head motion greater than half a voxel was deemed *a priori* to be unacceptable, and images meeting this criterion were to be excluded. None of the scans

acquired in this study had head motion exceeding this criterion, so all images were included in the analyses.

4.2.8.4 First-level analyses: Single-subject analyses

The following first-level analysis procedure applies to the fMRI data acquired for the pilot subject during the second pilot study (phase one), the FMS subjects and controls in phase two and the intervention and control group subjects (phase three). After pre-processing the data, individual subject data analysis was performed by linear regression of the fMRI data in FSL. For each of the participants four BOLD-contrast differences (t-contrasts) were determined as a function of BOLD-signal changes compared to the baseline condition (*Active>rest; Passive>rest; Active>Passive; Passive>Active*) according to the routine procedures implemented. The brain volumes collected during the 'on' conditions were compared with the brain volumes collected during the 'off' conditions using Students' *t test.* Resultant Z statistical volumes and mean differences volumes were registered into standardized space using the statistical parametric mapping (FSL) echo-planar imaging template and re-sliced to 2 mm^3 voxels. Anatomic regions were identified (i) by inspection of individual functional images superimposed on an individual's structural image; and (ii) by conversion of the coordinates to the coordinate system of the Montreal Neurological Institute (MNI) atlas and localization using this atlas and automated software. The scans were registered to high resolution MNI structural scans so that the FSL atlas tools could be used to correctly locate these regions of interest (ROI's). Statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of p=0.05 (Worsley., 2001). The threshold is indicated with the use of a "ramp" i.e. *2.3*  *8.0*

4.2.8.5 Higher-level analyses (between groups) – Phase 2 and 3

The single-subject analyses formed the basis for the higher-level analysis of the subject/control fMRI data. Higher-level analyses of the subject fMRI data was also conducted in FSL.

Mean baseline activation of functional within-groups and between-groups were analyzed for the FMS subjects and the healthy controls (phase 2). Mean baseline and post-intervention activation of functional areas were analyzed for the intervention and control groups (phase 3). The contrast of interest was the active>passive condition (where the brain activations for the passive condition were subtracted from the active condition), since it was expected that significant activation during this condition could signify association with the construct of interest *viz.* pain catastrophization. Anatomical localization of activated brain regions was determined by reference to the atlas tool automatically implemented in FSL. Paired *t- test* for comparison of two dependent samples and contrasts was used. Statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of p=0.05 (Worsley., 2001). The threshold is indicated with the use of a “ramp” i.e.

2.3  *8.0.*

4.2.8.6 Other data

The open-ended questions of the post-treatment survey were qualitatively analyzed and the closed-ended questions were quantitatively analyzed using frequency counts. Mean pre- and post-session (intervention group), as well as mean pre- and post-treatment (intervention and control group) PCS and TSK scores were analyzed and compared between the groups and within-subjects for preliminary efficacy of the intervention.

4.3 Results

4.3.1 PHASE ONE: Development and validation of fMRI visual task

4.3.1.1 Pilot study one

4.3.1.1.1 Subject description

The pilot subject was a 40-year-old coloured South African female with a four-year history of FMS. The subject, a divorced and single mother of three children under the age of 18 years, resided in the Cape Metropole (Western Cape, South Africa) and was permanently employed as an administrator. Her highest education level was a college diploma. The subject was English-speaking.

4.3.1.1.2 Activity level

The subject reported an activity level of 2 on the GPPAQ ("sitting most of the day"), with an average of 32 hours of activity per week and an average walking speed.

4.3.1.1.3 Medical and FMS history

The subject reported that the most common FMS symptom experienced was pain, and that the pain was mostly experienced in the lower back and chest area. The severity of the pain was reported as "severe" (4 on the pain severity scale). Symptoms were experienced once a week, and were increased by sweeping/mopping/vacuuming, cleaning the house, washing/brushing hair, dressing/undressing, bathing/showering and exercising. At the time of the study the subject was taking medication for her pain. The subject had previously undergone a hysterectomy. The subject reported no previous history of substance abuse or of being institutionalized in a mental facility. The subject reported no conditions which were contraindicated for fMRI scanning.

4.3.1.1.4 Self-reported patient outcomes

The pilot subject scored 27 on the SA-PCS and 64 on the SA-TSK. For the subsections of the SA-FIQR, the subject scored as follows: subsection A: 40; subsection B: 10; and subsection C: 36 (total SA-FIQR score reported: 86).

4.3.1.1.5 Result of pilot study 1

Following the fMRI scanning procedure, the pilot subject was required to comment (using a specifically-designed form) on the instructions provided prior to the fMRI scanning procedure, the overall duration of procedure, the overall procedure and the overall presentation of the visuals. The subject reported that the instructions provided prior to the fMRI scanning session were clear and she understood what was expected of her and what she could expect during the fMRI scanning procedure. Regarding the overall duration of the procedure, the subject felt that the procedure was slightly too long. Regarding the visuals, the subject was able to clearly decipher what each visual was depicting, but felt that the black and white visuals became “quite boring” when exposed to the visuals for the entire duration of the scanning procedure. The subject also specifically asked that a couple of the visuals be removed as they were “quite depressing”. Overall, the subject felt that the visuals needed to be made more exciting and that colour in the visuals needed to be retained to keep the person being exposed to the visuals for the duration of the scanning procedure interested.

The following changes were made to the initial fMRI visual task and procedure:

- All visuals were reverted back to their original colour.
- The duration of the rest period was reduced from 30 s to 20 s. In total, the duration of the entire fMRI task was reduced by 2 minutes (from 12 minutes to 10 minutes).
- The visuals which were reported to make the subject feel depressed were removed from the task list.

4.3.1.2 Focus group study

4.3.1.2.1 Subjects' demographic characteristics

A total of 16 FMS subjects agreed to participate in the focus group study. In Table 4.2, the demographic information for the included subjects is depicted.

Table 4.2: Demographic characteristics of focus group (n=16)

Variable	Focus group
Gender	Female
Age (yrs) mean±SD	49.25±7.33
Ethnicity	
Coloured	13
Black	2
White	1
Language	
English	5
Afrikaans	9
Xhosa	2
No. of children mean±SD	2.87±1.06
Marital status	
Married	7
Divorced	3
Separated	2
Widowed	2
Single	2
Highest level of education	
< grade 7	2
> grade 12	10
Matric	3
Tertiary education	1
Employment status	
Unemployed	5
Permanently Employed	2
Casually employed	1
Self-employed	0
Housewife	4
Pensioner	1
Disability grant	2
No. of years living with FMS mean±SD	4.23±2.67
PCS score mean±SD	41.68±6.75
TSK score mean±SD	49.38±7.29
FIQR scores mean±SD	
Subscale A	64.75±10.49
Subscale B	13.76±3.79
Subscale C	72.00±7.34
No. of physical active hours/week mean±SD	9.18±5.56

4.3.1.2.2 Results of focus group study

A total of 22 visuals (13 active and nine passive visuals) were presented to the focus group on a laptop via a MS PowerPoint Presentation slideshow. The subjects had to report their feelings and thoughts towards each visual presented on the form provided (Appendix 11). Some subjects reported more than one feeling/thought per visual. Based on the results obtained, visuals were either retained to be used as part of the final fMRI task or discarded. The visuals, a description of the activity, the subjects' reported feelings/thoughts for each visual, any events (negative or unexpected) related to a particular visual and the decision to retain or discard the visuals are listed in Table 4.3. For each reported feeling/thought, the total number of subjects of the 16 included subjects who reported that specific feeling/thought for that specific visual is indicated, as well as the percentage value.

- *Visuals discarded following focus group session*

It was anticipated that the visuals of the exercise activities would elicit feelings/thoughts of pain; and that visuals of passive/relaxing activities would elicit feelings of happiness/relaxation. The focus group session however revealed some unexpected results. Visual #9 was discarded based on the fact that four subjects (25%) were reminded of their sleeping disorders (which were related to the FMS) when looking at a visual of a person napping (which was a passive/relaxing activity). Visual #22 was discarded since six subjects (37.5%) reported that they felt/thought of suicide when looking at the visual of a woman sitting alone at the beach (which was a passive/relaxing activity). Visual #19 was discarded since two subjects (12.5%) unexpectedly reported that the visual of the person skipping (which was an exercise activity) reminded them of their childhood and this made them feel happy. Of the 22 visuals presented to the focus group, seven passive visuals (visuals #2,5,6,8,12, 16 and 18) and 12 active visuals (visuals # 1,3,4,7,10,11,13,14,15,17,20 and 21) were retained. Of these retained visuals, six passive and six active visual were selected and used in the fMRI task during the second pilot study.

Table 4.3: Results from the focus group session (n=16)

			Subjects' responses; Total no /16 (%)						
No.	**Description of activity**	**Type of activity**	**Feel Happy**	**Feel Relaxed**	**Feel Nothing**	**Feel Pain**	**Feel Sad/depressed**	**Related event**	**Final decision**
1	Doing aerobics exercises	Active				16 (100)			Retained
2	Bathing in bubble bath	Passive	13 (81.25)	16 (100)					Retained
3	Bridging exercise	Active				16 (100)			Retained
4	Cycling	Active				16 (100)			Retained
5	Drinking tea	Passive	2(12.5)	12 (75)	2 (12.5)				Retained
6	An island holiday	Passive	10 (62.5)	14 (87.5)					Retained
7	Doing back leglifts	Active				16 (100)			Retained
8	Receiving a massage	Passive	14 (87.5)	16 (100)					Retained
9	Taking a nap	Passive	4 (25)	5 (31.25)	7 (43.75)		4 (25)	Sleeping disorders	Discarded
10	Playing tennis	Active				16 (100)			Retained
11	Running	Active				16 (100)			Retained
12	Walking on beach	Passive	14 (87.5)	12 (75)					Retained
13	Stretching	Active				16 (100)			Retained
14	Doing front leglifts	Active				16 (100)			Retained
15	Doing squats	Active				16 (100)			Retained
16	Watching TV	Passive		9 (56.25)	7 (43.75)				Retained
17	Doing lunges	Active				16 (100)			Retained
18	Reading a book	Passive	9 (56.25)	4 (25)	4 (25)				Retained
19	Skipping	Active	2 (12.5)			14 (87.5)		Childhood days	Discarded
20	Going up stairs	Active				16 (100)			Retained
21	Doing sit-ups	Active				16 (100)			Retained
22	Sitting at beach alone	Passive	5 (31.25)	4 (25)	3 (18.75)		6 (37.5)	Suicide	Discarded

4.3.1.3 Pilot study two

The same subject used in the first pilot study was used in the second pilot study. Based on the results of the first pilot study and the focus group study, a set of visuals were selected to be used in the fMRI task during pilot study two. Active visuals thought to best provoke the construct of interest *viz.* pain catastrophization, and no other negative connotations, were selected. Full colour versions of the visuals were retained instead of converting the visuals to black and white, as previously done in the first pilot study. The same fMRI procedure described in pilot study one was followed, except that the visuals differed and the duration of the rest period differed (by 10 s). The subject was once more exposed to the visuals of active and passive activities during the fMRI scan.

4.3.1.3.1 fMRI data

The analysis of the fMRI acquired for the subject in pilot study two was conducted to ensure that the expected functional brain areas when exposed to various visuals were elicited such as the visual cortex situated in the occipital lobe. The results of the fMRI analyses for the pilot subject during second pilot study were as follows:

- *Active>rest condition (where the brain activations during the rest period were subtracted from the active condition)*

In figure 4.8, a screenshot of the brain partitions (slices) acquired during the active>rest condition is provided, indicating the functional areas significantly activated for the pilot subject during the second pilot study:

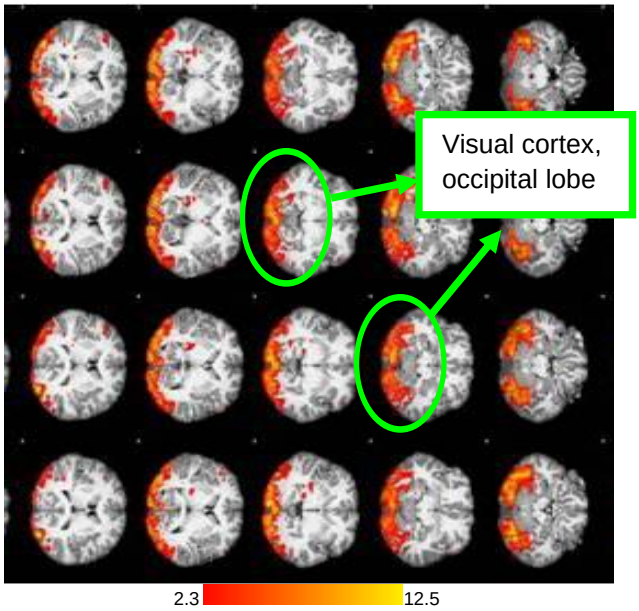


Figure 4.8: A screenshot of the brain partitions (slices) acquired during the active>rest condition indicating the functional areas significantly activated (p<0.05) i.e. the visual cortex situated in the occipital lobe (indicated by the green circles), for the pilot subject

It is clear from the image above (figure 4.8) that the visual cortex, situated in the occipital lobe, was significantly activated ($p<0.05$) and dominated during the active>rest condition for the pilot subject during the second pilot study.

- *Passive>rest condition (where the brain activations during the rest period were subtracted from the passive condition)*

In figure 4.9, a screenshot of the brain partitions (slices) acquired during the passive>rest condition is provided, indicating the functional areas significantly activated for the pilot subject during the second pilot study:

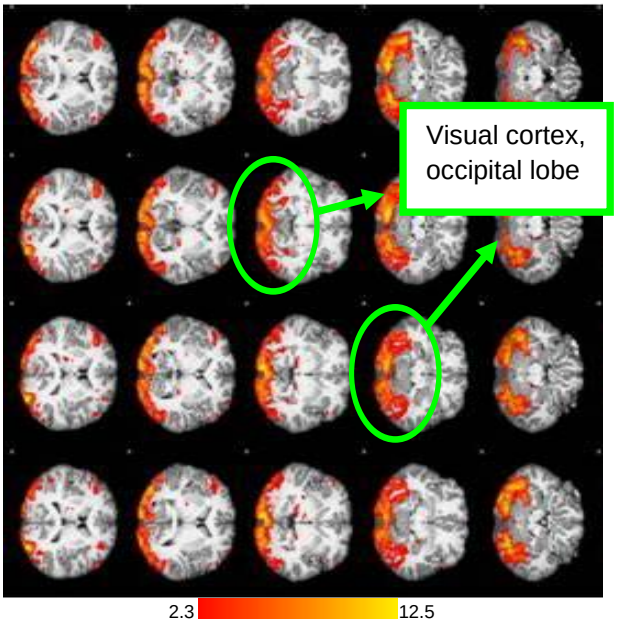


Figure 4.9: A screenshot of the brain partitions (slices) acquired during the passive>rest condition indicating the functional areas significantly activated (p<0.05) i.e. the visual cortex situated in the occipital lobe (indicated by green circles), for the pilot subject.

It is clear from the image above (figure 4.9) that the visual cortex, situated in the occipital lobe, was significantly activated ($p<0.05$) and dominated during the passive>rest condition for the pilot subject during the second pilot study.

- *Active>passive condition (where the brain activations during the passive condition were subtracted from the active condition)*

In figure 4.10, a screenshot of the brain partitions (slices) acquired during the active>passive condition is provided, indicating the functional areas significantly activated for the pilot subject during the second pilot study:

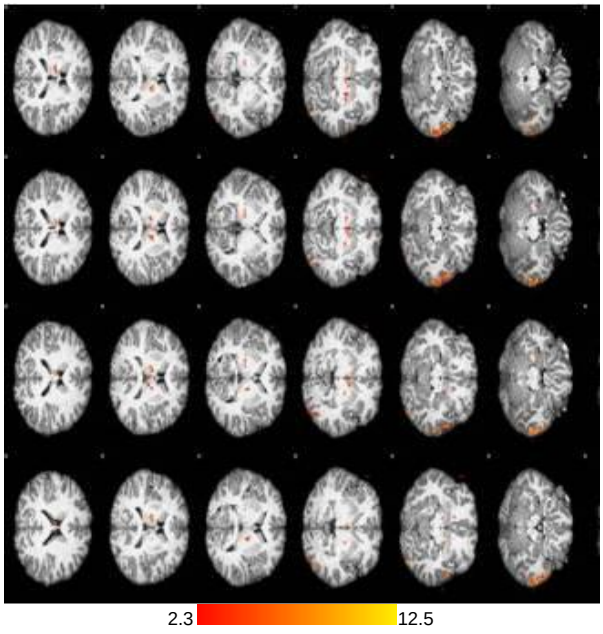


Figure 4.10: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the functional areas significantly activated (p<0.05) for the pilot subject.

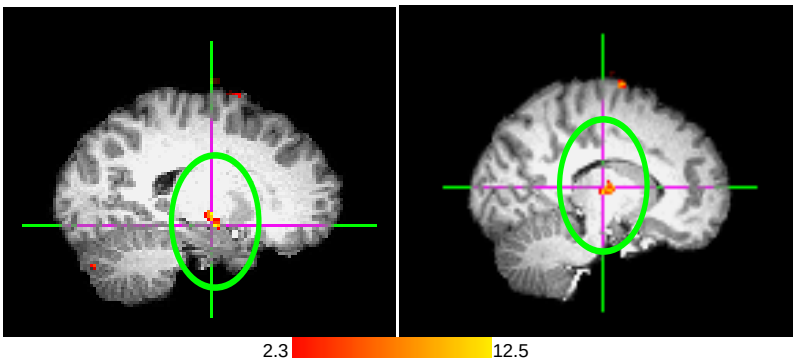
In Table 4.4, the Z co-ordinates (x, y and z), Z-scores as well as *p*-values for all the areas significantly activated (p<0.05) during the active>passive condition for the pilot subject during the second pilot study are provided.

Table 4.4: Functional areas significantly activated (*p<0.05)* during the active>passive condition for the pilot subject

Functional brain areas	x	y	z	Z-score	P value
R Superior temporal gyrus	46	28	8	4.12	<0.0000
R Cerebellum, posterior lobe	39	19	0	4.46	<0.0000
R Inferior frontal gyrus	18	38	10	3.84	<0.0000
R Occipital lobe	41	11	10	4.5	0.00019
R Amygdala	24	32	0	3.53	0.000273
R Insular cortex	41	32	5	4.36	0.00121
R Thalamus	26	32	9	4.00	0.00264
R Superior parietal lobule	21	17	18	3.34	0.0059

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

In figure 4.11, an enlarged image of the significantly activated (p<0.05) functional brain areas indicated in figure 4.10 is provided clearly indicating the activation of the R amygdala and the R thalamus during the active>passive condition for the pilot subject:



R Amygdala (24 32 0) ***R Thalamus (26 32 9)***

Figure 4.11: Screenshots of the brain partitions (slices) acquired during the active>passive condition indicating the specific functional areas (R amygdala and R thalamus) significantly activated (p<0.05) for the pilot subject.

- *Passive>active condition (where the brain activations during the active condition were subtracted from the passive condition)*

In figure 4.12, a screenshot of the brain partitions (slices) acquired during the passive>active condition is provided, indicating the functional areas significantly activated (p<0.05) for the pilot subject:

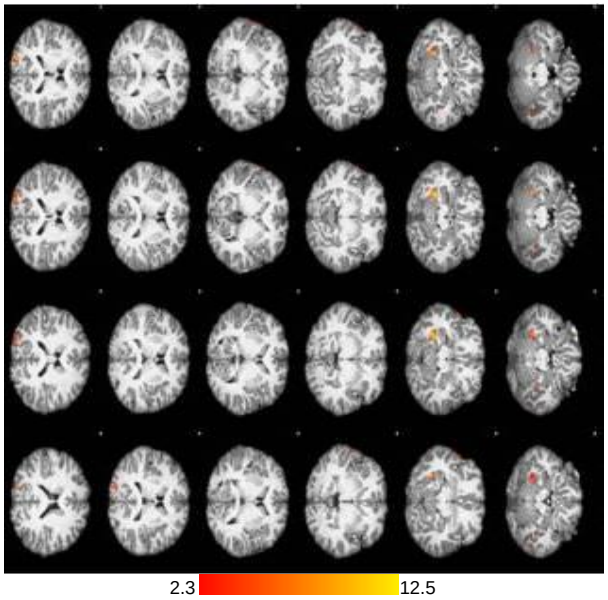


Figure 4.12: A screenshot of the brain partitions (slices) acquired during the passive>active condition indicating the functional areas significantly activated (p<0.05) for the pilot subject.

In Table 4.5, the Z co-ordinates (x, y and z), Z-scores as well as *p*-values for all the areas significantly activated (p<0.05) during the passive>active condition for the pilot subject during the second pilot study are provided.

Table 4.5: Functional areas significantly activated (*p<0.05)* during passive>active condition for the pilot subject

Functional areas	x	y	z	Z-score	P value
R Precuneous cortex	28	17	19	3.77	<0.0000
R Superior and middle temporal gyrus	43	25	6	3.47	0.000133
R Thalamus	26	25	8	4.74	0.000393
R Occipital lobe	27	11	11	3.77	0.00121
R Frontal lobe	26	46	10	3.85	0.00264
R Precentral gyrus	17	33	13	3.92	0.00394

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

At the end of the second pilot study, the pilot patient, the principal researcher, as well as the supervisors, were satisfied with the changes made, as well as with the processing of the pilot subject data and the output of the data, and no further changes to the fMRI task were therefore required.

4.3.2 PHASE TWO: fMRI EXPLORATORY STUDY

4.3.2.1 fMRI study

4.3.2.1.1 Subject description

A total of 13 FMS subjects and nine matched healthy controls participated in phase two of this study. In Table 4.6, a comparison of the sociodemographic information for the FMS subject group and control group at baseline is depicted:

Table 4.6: Baseline comparison of sociodemographic characteristics of FMS subjects and matched controls

Variable	**FMS subjects**	**Matched Controls**	***p***
	N=13	**N=9**	
Gender	Female	Female	
Age (yrs) mean±SD	46.00±9.72	48.22±14.77	>0.05
Number of children	2.75±1.14	2.75±0.88	>0.05
Marital status			
Single	2	1	
Married	6	5	
Separated	2	0	
Divorced	2	2	
Widowed	1	1	
Years living with FMS mean±SD	3.81±2.27	NA	
Ethnicity			
Coloured	9	6	
Black	4	3	
White	0	0	
Language			
English	2	1	
Afrikaans	6	5	
Xhosa	4	3	
Level of education			
< grade 7	5	4	
> grade 12	4	2	
Matric	3	2	
Tertiary education	1	1	
Employment status			
Unemployed	6	1	
Permanently employed	0	5	
Self-employed	2	0	
Casually employed	1	0	
Pensioner	1	1	
Housewife	2	2	
Disability grant	1	0	
Physical activity hours/week mean±SD	9.62±6.79	39.44±12.61	<0.0000†

Key: NA=not applicable, SD=standard deviation, †=significant (p<0.05)

All subjects were female and South African, and lived in the surrounding areas within the Cape Metropole. One FMS subject withdrew from the study shortly before the fMRI scans took place. Baseline sociodemographic data were however included for this subject along with the rest of the subjects (Table 4.6). There were no significant differences (p>0.05) in age and number of children between the FMS subject group and the matched control group. There was however a significant difference in number of physical active hours per week (p<0.0000) between the two study groups (Table 4.6).

4.3.2.1.2 fMRI results

Within-group analyses of baseline fMRI data were conducted to identify the mean activation in both the FMS subject group and the matched control group. Between-group analyses of baseline fMRI data were conducted to indicate mean activation differences between the FMS subject group and the matched control group. The results were as follows:

- *Within-group analysis at baseline during the active>passive condition*

Mean activation in FMS subject group

On average, the following functional areas were significantly activated ($p<0.05$) during the active>passive condition in the FMS subject group at baseline (figure 4.13):

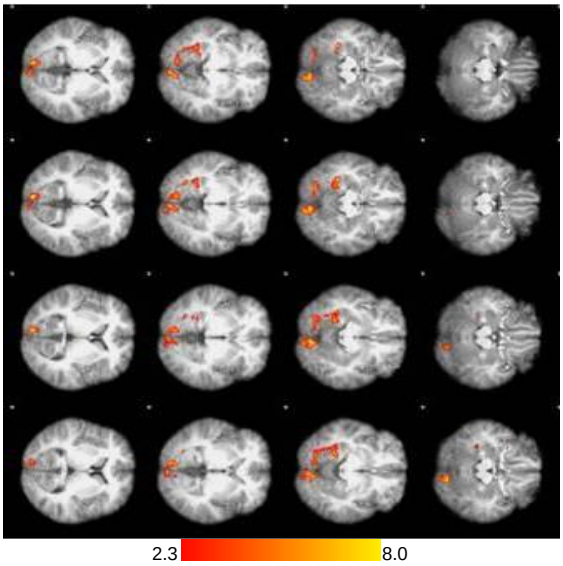


Figure 4.13: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the functional areas significantly activated ($p<0.05$) for the FMS subject group at baseline.

In table 4.7, the Z co-ordinates (x, y and z), Z-scores as well as *p*-values for all the areas significantly activated ($p<0.05$) during the active>passive condition in the FMS subject group at baseline are provided.

Table 4.7: Mean functional areas significantly activated (p<0.05) during the active>passive condition in the FMS subject group at baseline

Functional brain areas	Co-ordinates MNI (FSL)			Z-score	P-value
	x	y	z		
R Inferior Temporal gyrus, R Cerebellum posterior lobe	47	-61	-22	5.26	<0.0000
R Inferior and middle frontal gyrus	42	10	23	4.29	<0.0000
L Inferior frontal gyrus	-44	24	14	3.6	<0.0000
L Superior parietal lobe, L Supramarginal gyrus	-29	-54	53	3.8	<0.0000
L Thalamus	-23	-29	-9	4.31	0.00113

KEY: MNI = Montreal Neurological Institute; L = Left, R = Right

Mean activation in matched control group

On average, the following functional areas were significantly activated (p<0.05) during the active>passive condition in the matched control group at baseline (figure 4.14):

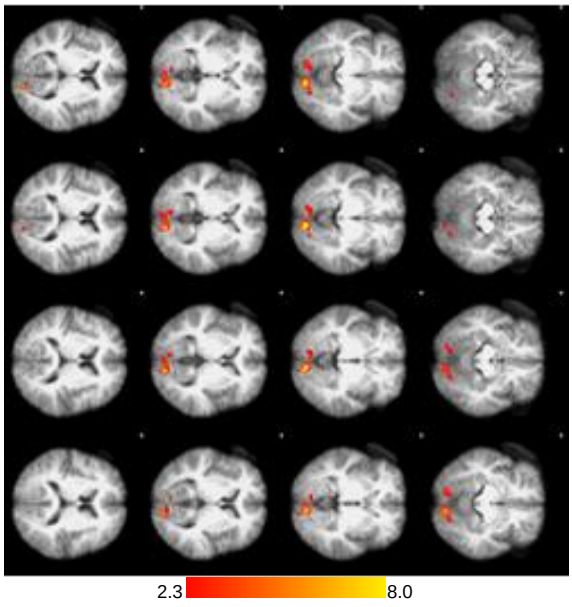


Figure 4.14: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the functional areas significantly activated* (p<0.05) *for the matched control group at baseline.

In Table 4.8, the Z co-ordinates (x, y and z), Z-scores as well as *p*-values for all the areas significantly activated (p<0.05) during the active>passive condition in the matched control group are provided.

Table 4.8: Mean functional areas significantly activated (p<0.05) during the active>passive condition in the matched control group

Functional area	Co-ordinates MNI (FSL)			Z-score	P value
	X	Y	Z		
R Temporal fusiform gyrus	48	-75	0	4.35	<0.0000
R Inferior parietal lobe	31	-48	56	3.07	0.00247

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

- *Between-group activation during the active>passive condition*

The mean differences in activation of the functional brain areas between the two groups, the FMS subject group and the matched control group, was analyzed. The images from the functional data analyses in figure 4.15A and 4.15B illustrate the significant differences (p<0.05) in functional brain area activation during the active>passive condition between the FMS subject group and the matched control group:

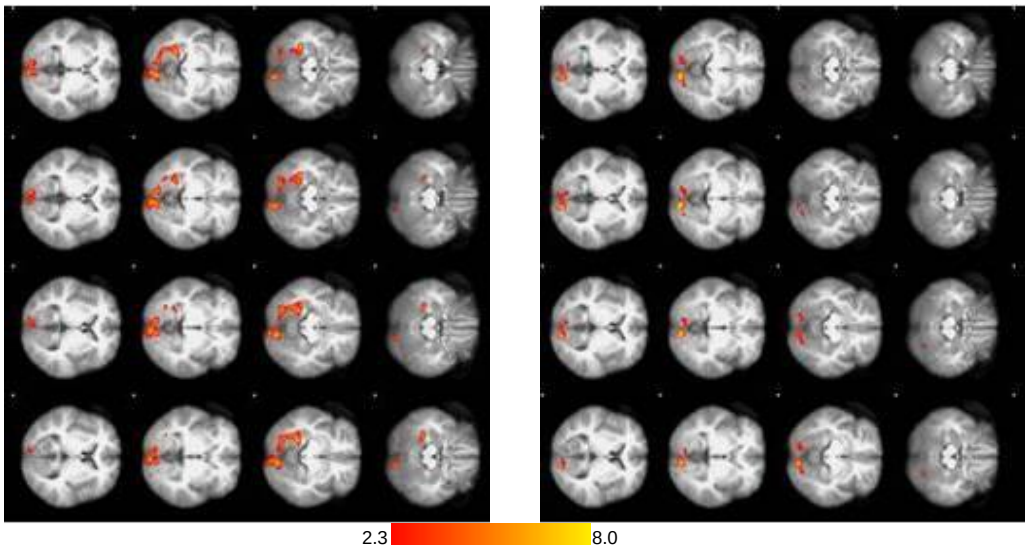


Figure 4.15 (A and B): Between group comparison of significant activation (p<0.05) of functional areas during the active>passive condition

Figure 4.15 indicates that significant activation (p<0.05) was found in more functional brain areas during the active>passive condition for the FMS subject group compared to the matched control group.

In Tables 4.9 and 4.10, the Z co-ordinates (x, y and z), Z-scores as well as p-values for all the areas significantly activated (p<0.05) during the active>passive condition for the FMS subject group and matched control group are provided. Table 4.9 depicts the differences in activation of the functional brain areas where the brain activations acquired for the matched control group were subtracted from the brain activations acquired for the FMS subject group during the active>passive condition (FMS subjects>matched controls). Table 4.10 depicts the differences in activation of the functional brain areas where the brain activations acquired for the FMS subject were subtracted from the brain activations acquired for the matched controls group during the active>passive condition (matched controls>FMS subjects).

Table 4.9: Significant differences (p<0.05) in functional area activation for FMS subjects>matched controls contrast during the active>passive condition:

Functional area	Co-ordinates MNI (FSL)			Z-score	p-value
	x	y	z		
R Inferior temporal gyrus, R Cerebellum posterior lobe	47	-61	-22	5.26	<0.0000
R Inferior and middle frontal gyrus	42	10	23	4.29	<0.0000
L Inferior frontal gyrus	-44	24	14	3.6	<0.0000
L Superior parietal lobe, L Supramarginal gyrus	-29	54	53	3.8	0.0003
L Thalamus	-23	-29	9	4.31	0.00929

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

Table 4.10: Significant differences (p<0.05) in functional area activation for matched controls>FMS subjects during the active>passive condition:

Functional area	Co-ordinates MNI (FSL)			Z-score	p-value
	x	y	z		
R Fusiform gyrus	41	-70	-11	4.79	<0.0000

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

4.3.3 PHASE 3: VRET study

4.3.3.1 Subject sociodemographic characteristics

A total of 12 FMS subjects participated in phase three of this study. The subjects were retained from phase two of this study. Six subjects were allocated to the intervention/VRET group and six subjects were allocated to the control group/waiting list. The baseline data including the sociodemographic information, GPPAQ, SA-PCS, SA-TSK and SA-FIQR were retained for all subjects from phase two of this study. A baseline comparison of the demographic information of the two groups is provided in Table 4.11:

Table 4.11: Baseline comparison of demographic characteristics between the subjects in the Intervention and Control group

Variable	Intervention group N=6	Control group N=6	*p*
Gender	Female	Female	
Age (yrs) mean±SD	44.7±7.8	44.9±8.9	>0.05
Ethnicity			
Coloured	4	3	
Black	2	3	
White	0	0	
Language			
English	1	2	
Afrikaans	3	1	
Xhosa	2	3	
No. of children	3.00±1.22	2.67±1.21	>0.05
Marital status			
Married	3	3	
Divorced	1	1	
Separated	1	1	
Widowed	0	0	
Single	1	1	
Level of education			
< grade 7	3	2	
> grade 12	2	2	
Matric	1	2	
Tertiary education	0	0	
No. of years living with FMS mean±SD	4.83±2.17	5.08±2.69	>0.05
SA-PCS score mean±SD	39.83±5.98	40.83±5.74	>0.05
SA-TSK score mean±SD	47.67±8.71	48.67±4.13	>0.05
SA-FIQR scores mean±SD			
Subscale A	59.33±13.84	61.50±21.74	>0.05
Subscale B	14.00±5.83	12.50±5.24	>0.05
Subscale C	69.00±8.37	73.00±8.74	>0.05
No. of physical active hours/week mean±SD	9.33±7.92	10.07±6.50	>0.05

There were no significant differences (p>0.05) in age, number of children, number of years living with FMS, SA-PCS scores, SA-TSK scores, SA-FIQR scores, and number of physical active hours per week, for the two study groups at baseline.

4.3.3.2 Subjective outcome measurement data

Subject outcomes namely pain catastrophization and kinesiophobia using the SA-PCS and SA-TSK, respectively, were measured at baseline and post-intervention for the intervention

group and the control group. Baseline outcome data were collected for 12 subjects (six in the intervention group and six in the control group. Post-intervention data were for 10 subjects (five in the intervention group and five in the control group). One subject in the intervention group was lost to follow-up since her husband passed away shortly after she underwent her first scan. She did not want to come to the hospital (or a hospital setting like CUBIC) at all, and therefore did not even begin the intervention. One subject in the control group was lost to follow-up as she had moved from her last known address and did not leave a forwarding address. Post-intervention scans and subjective outcome measure data could not be obtained for these two subjects. The time period between the two outcome measurements was three to eight weeks. The reason for this discrepancy in the time period between outcome measurements was due to the fact that not all subjects were immediately available for the post-intervention measurement at the end of the intervention. Differences between baseline and post-intervention outcomes for the intervention and control group (phase 3) were as follows (Table 4.12):

Table 4.12: Differences between baseline and post-intervention outcomes for the intervention and control group

Outcomes per study group	**Baseline Mean±SD**	**Post-intervention Mean±SD**	**MD**	***p* for differences between groups**	
				At baseline	***Post-intervention***
SA-PCS				0.39	0.24
Intervention group n=6	40.0±5.5	35.2±6.7	-4.8		
Control group n=6	40.7±4.9	37.7±5.6	-3.0		
SA-TSK				0.43	0.27
Intervention group n=5	47.2±7.9	43.0±6.4	-4.2		
Control group n=5	48.3±5.62	46.4±11.4	-1.9		

KEY: MD=Mean difference

4.3.3.3 fMRI results

- *Within group differences at baseline*

The average activation of functional areas (within-group analyses) during the active>passive conditions for the intervention group at baseline was analyzed. On average the following functional areas were significantly activated (p<0.05) during the active>passive condition in the intervention group (n=6) at baseline (figure 4.16):

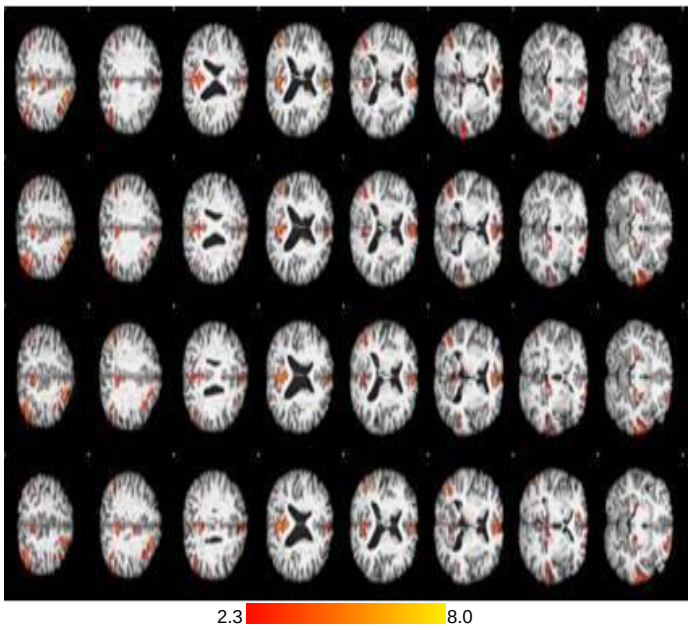


Figure 4.16: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the mean functional areas significantly activated (p<0.05) for the intervention group at baseline.

In Table 4.13, the Z co-ordinates (x, y and z), Z-scores as well as p-values for all the areas significantly activated (p<0.05) during the active>passive condition for the intervention group at baseline are provided.

Table 4.13: Mean significant functional area activation (p<0.05) for the intervention group during the active>passive condition (at baseline):

Functional area	Co-ordinates MNI (FSL)			Z-score	P value
	x	y	z		
R Insular cortex	38	36	23	7.09	<0.0000
R Cerebellum, anterior lobe	31	19	12	5.55	<0.0000
R Cerebellum, posterior lobe	39	13	15	5.83	<0.0000
R Cerebellum, posterior lobe	21	17	10	5.79	<0.0000
R Temporal lobe	45	32	9	4.39	<0.0000
R Parahippocampal gyrus	37	31	9	4.39	<0.0000
R Middle frontal gyrus	38	46	16	4.17	0.00135
R Corpus callosum	25	22	23	3.58	0.0194
R Thalamus	33	27	19	3.7	0.0194
R Supramarginal gyrus, middle temporal gyrus, Superior temporal gyrus	43	23	20	4.47	0.044

Key: BA = Brodmann area, MNI = Montreal Neurological Institute, L=Left, R=Right

On average the following functional areas were significantly activated (p<0.05) during the active>passive condition in the control group (n=5) at baseline (figure 4.17):

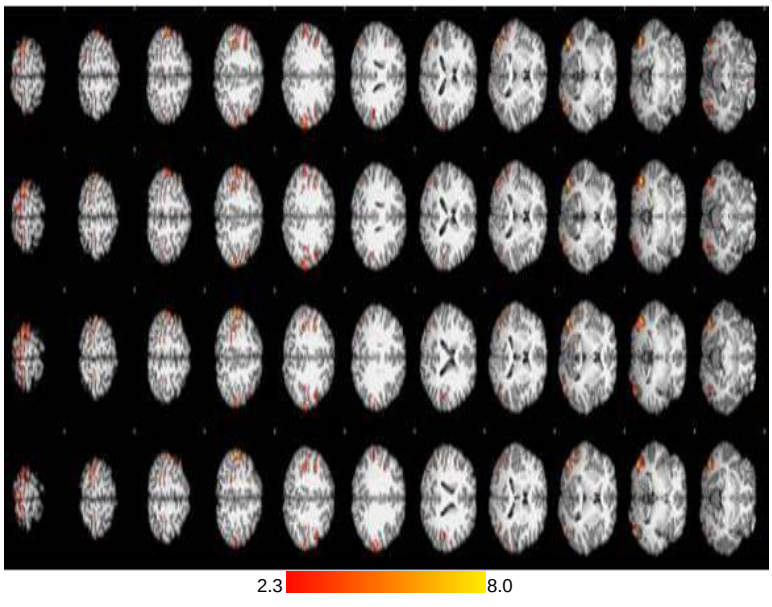


Figure 4.17: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the mean functional areas significantly activated (p<0.05) for the control group at baseline.

In Table 4.14, the Z co-ordinates (x, y and z), Z-scores as well as *p*-values for all the areas significantly activated ($p<0.05$) during the active>passive condition for the control group at baseline are provided.

Table 4.14: Mean significant *(p<0.05)* functional area activation for the control group during active>passive condition (at baseline):

Functional areas	Co-ordinates MNI (FSL)			Z-MAX	P
	x	y	z		
R Supramarginal gyrus	19	24	21	5.51	6.05e-24
R Cerebellum anterior lobe	22	17	8	6.59	6.56e-15
R Superior and middle temporal gyrus	46	23	19	5.47	1.04e-10
R Cerebellum posterior lobe	42	15	7	5.12	1.22e-09
R Insula	21	31	23	4.71	3.28e-06
R Cerebellum anterior lobe	22	25	7	5.62	0.000341
R Precentral gyrus, central operculum gyrus	42	31	21	3.98	0.00253
R Middle frontal gyrus	37	44	14	3.53	0.0355

Key: BA = Brodmann area, MNI = Montreal Neurological Institute, L=Left, R=Right

- *Within group differences post-intervention*

On average the following functional areas were significantly activated ($p<0.05$) during the active>passive condition in the control group (n=5), post-intervention (figure 4.18):

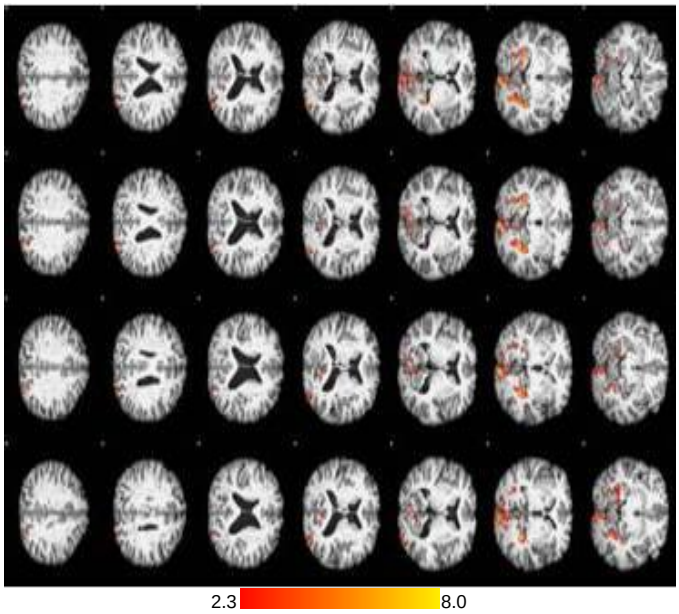


Figure 4.18: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the mean functional areas significantly activated (p<0.05) for intervention group, post-intervention.

In Table 4.15, the Z co-ordinates (x, y and z), Z-scores as well as *p*-values for all the areas significantly activated ($p<0.05$) during the active>passive condition for the intervention group post-intervention are provided.

Table 4.15: Mean significant functional area activation for the intervention group during the active>passive condition (post-intervention):

Functional areas	Co-ordinates MNI (FSL)			Z-MAX	P
	x	y	z		
R Cerebellum Anterior lobe	32	15	6	6.03	3.33e-12
R Cerebellum Posterior lobe	38	15	10	4.04	1.61e-06
R Cerebellum Anterior lobe	37	25	9	6.22	1.2e-05

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

On average the following functional areas were significantly activated ($p<0.05$) during the active>passive condition in the control group (n=6), post-intervention (figure 4.19):

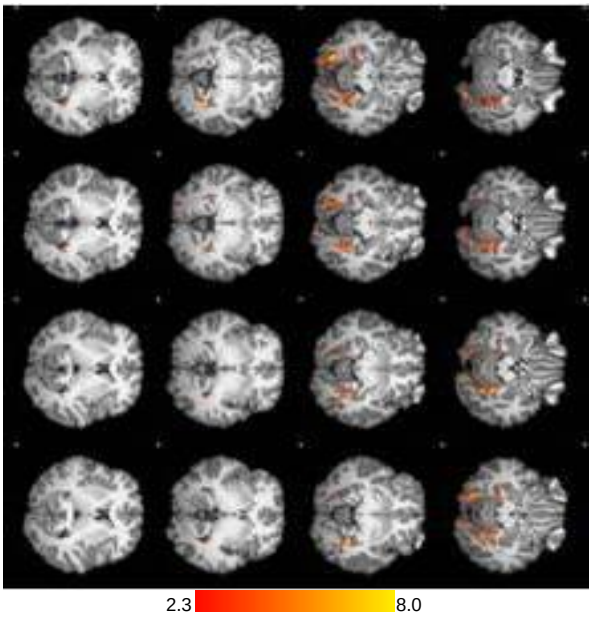


Figure 4.19: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the mean functional areas significantly activated (p<0.05) for the control group, post-intervention.

In table 4.16, the Z co-ordinates (x, y and z), Z-scores as well as *p*-values for all the areas significantly activated (*p*<0.05) during the active>passive condition for the control group post-intervention are provided.

Table 4.16: Mean significant (p<0.05) functional area activation for the control group during active>passive condition (post-intervention):

Functional area	Co-ordinates MNI (FSL)			Z-score	P value
	x	y	z		
R Inferior temporal gyrus	41	26	10	5.18	5.81e-12
R Cerebellum anterior lobe	28	19	6	4.49	7.15e-07

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

- *Between-group differences (post-intervention)*

The mean difference in activation of the functional brain areas between the two groups (intervention and control groups) was analyzed. The images from the functional data

analyses in figure 4.20 illustrate the significant differences (p<0.05) in functional brain area activation during the active>passive condition between the intervention and control groups.

The following functional areas were significantly activated (p<0.05) during the active>passive condition where intervention group>control group (where the brain activations acquired for the control group were subtracted from the brain activations acquired for the intervention group), post-intervention (figure 4.20):

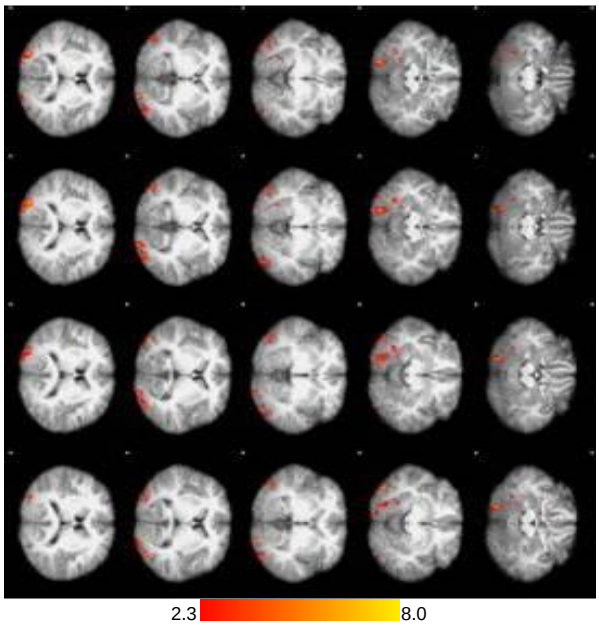


Figure 4.20: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the mean functional areas significantly activated (p<0.05) where the intervention group>control group, post-intervention.

In Table 4.17, the Z co-ordinates (x, y and z), Z-scores as well as p-values for all the areas significantly activated (p<0.05) during the active>passive condition where the intervention group>control group, post-intervention are provided:

Table 4.17: Mean significant functional area activation where the intervention group>control group during the active>passive condition (post-intervention):

Functional areas	Co-ordinates MNI (FSL)			Z-MAX	P
	x	y	z		
R Cerebellum Posterior Lobe	21	-84	-15	3.82	<0.0000
R Cerebellum Posterior Lobe	47	-64	-26	3.29	0.0322

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

The following functional areas were significantly activated (p<0.05) during the active>passive condition where the control group>intervention group (where the brain activations acquired for the intervention group were subtracted from the brain activations acquired for the control group), post-intervention (figure 4.21):

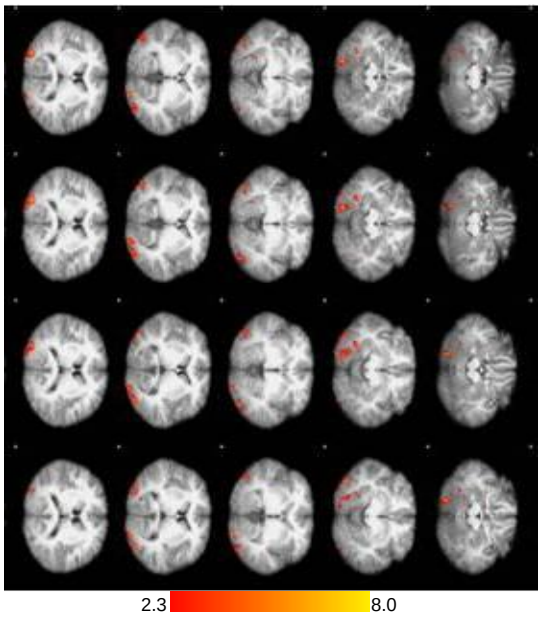


Figure 4.21: A screenshot of the brain partitions (slices) acquired during the active>passive condition indicating the mean functional areas significantly activated (p<0.05) where the control group> intervention group, post-intervention.

In Table 4.18, the Z co-ordinates (x, y and z), Z-scores as well as p-values for all the areas significantly activated (p<0.05) during the active>passive condition where control group>intervention group, post-intervention are provided.

Table 4.18: Mean significant *(p<0.05)* functional area activation where the control group>intervention group during the active>passive condition (post-intervention):

Functional areas	Co-ordinates MNI (FSL)			Z-score	P value
	x	y	z		
R Cerebellum anterior lobe	34	-50	-27	3.33	<0.0000
R Lateral occipital cortex	31	-90	28	3.38	<0.0000
R Lateral occipital cortex	45	-80	-11	3.54	0.00011
R Superior parietal lobe	21	-58	60	3.28	0.0259
L Inferior and middle frontal gyrus	-51	38	9	3	0.0275

Key: MNI = Montreal Neurological Institute, L=Left, R=Right

4.3.3.4 Feasibility/logistics of VRET intervention

Information pertaining to the following was collected from the five subjects allocated to the intervention group post-intervention using a datasheet designed by the principal researcher (Appendix 11): adverse effects; duration of session/intervention, ease of use and acceptability. The post-intervention survey was not however formally conducted.

The results of the post-intervention survey were as follows:

- No subjects in the intervention group reported any adverse effects to the VR equipment.
- When asked if the VR equipment was easy to use, all the subjects in the intervention group (n=5) reported that the equipment was easy to use and that they had no problems understanding what was expected of them.
- When asked if they felt that the duration of sessions were too long, four subjects replied that they did not feel that the individual sessions were too long. One felt that the individual sessions were a little too long as she was not doing much but “watching the videos”.
- When asked if they felt that the duration of the entire intervention was too long, all five subjects felt that the intervention was too long and that it took up a lot of their time. Having to come to the hospital for three weeks, twice a week was not easy for

them to do, even though they were being remunerated for transport fares. They all felt the intervention could have been shortened.

- When asked if they found the intervention applicable and appropriate, all the subjects understood the purpose of the intervention and replied that they felt that the intervention was applicable and appropriate. One subject however commented that seeing that she was just watching “videos” all the time, if the intervention could not be given to her on a CD or DVD and then she could watch them at home.

4.4 Chapter summary

- The development of the fMRI task was not straightforward and required various preliminary steps and meticulous planning.
- During the first pilot study and the focus group session, various unexpected reactions were reported towards the initial visuals selected for the fMRI task.
- The fMRI results for the pilot subject provided preliminary support that the fMRI visual task developed may have been appropriate for use in the subsequent studies.
- Significant activation (p<0.05) was found for the pilot subject in the visual cortex, right (R) insular cortex, R posterior cerebellum, R amygdala and the R inferior frontal gyrus during the active>passive condition (phase 1)
- Significant activation (p<0.05) was commonly found for the pilot subject during both conditions (active>passive/passive>active conditions) in the R thalamus (phase 1)
- Significant activation (p<0.05) was found exclusively for the FMS subject group, and not the matched control group, during the active>passive condition in the R inferior frontal gyrus, R posterior cerebellum, left (L) thalamus and R middle frontal gyrus (phase 2)
- At baseline, during the active>passive conditions, the intervention group showed significant activation (p<0.05) in the R insular cortex, R anterior and posterior cerebellum, R parahippocampal gyrus, R middle frontal gyrus, R corpus callosum, R thalamus, R supramarginal gyrus and the R middle and superior temporal gyrus.
- The control group showed significant activation (p<0.05) in the R anterior and posterior cerebellum, R middle and superior temporal gyrus, R middle frontal gyrus, R insular cortex, R supramarginal gyrus and the R precentral gyrus.
- The common functional areas significantly activated (p<0.05) during the active condition for both the intervention and controls groups were the R anterior and posterior cerebellum, R supramarginal gyrus, R insular cortex, R middle and superior temporal gyrus and the R middle frontal gyrus.
- Post-intervention, the intervention group continued to show significant activation (p<0.0000) in the R posterior cerebellum only.
- Post-intervention, the control group showed significant activation (p<0.0000) in the R anterior cerebellum, R superior parietal lobe, and L middle and inferior frontal gyrus.

CHAPTER FIVE

GENERAL DISCUSSION

5.1 Introduction

Currently, the role of pain catastrophizing is believed to be more pronounced in fibromyalgia syndrome (FMS) than in other rheumatologic chronic pain condition and is recognized as a barrier to the healthy re-establishment of psychological and physical functioning among patients with FMS (Hassett et al., 2000; Edwards et al., 2006; Rodero et al., 2008; Jones et al., 2009). Of concern is that in patients with FMS, the presence of pain catastrophization leads to fear-avoidance behaviours which often result in attrition from regular physical activity or non-compliance to prescribed exercise programs (Hassett et al., 2000; Edwards et al., 2006; Jones et al., 2009). Inactivity is particularly detrimental in FMS and typically leads to further complications such as deconditioning of the musculoskeletal system, increased pain, increased fatigue and functional disability (Oliver et al., 2002; Edwards et al., 2006; Jones et al., 2009). Poor compliance, as a result of pain catastrophization and fear-avoidance behaviours towards exercise and physical activity, among patients with FMS is therefore the primary factor contributing to the chronicity and accelerated deterioration of the condition (Ablin et al., 2010).

5.1.1 So why conduct this research?

The inference that pain catastrophization and subsequent fear-avoidance behaviours may influence the compliance of patients with FMS to exercise programs which in turn may affect the health of patients with FMS, justifies finding treatment approaches to alter pain catastrophization in the management of FMS (Turk et al., 2004; van Koulil et al., 2007; Garcia-Campayo et al., 2009). To date, research has been primarily focused on identifying the aetiology of FMS and on finding effective management strategies (Peterson et al., 2007;

Buskila et al., 2009). Despite the fact that effective management strategies such as exercise therapy for FMS symptoms may exist, their value in clinical practice is often diminished due to poor patient compliance (Cameron et al., 1995; Jones et al., 2009; Thomas et al., 2010; Gowans et al., 2010). Research focus has therefore shifted to try and identify predictors of poor treatment compliance in FMS and to target these predictors in an attempt to improve compliance toward management programs such as prescribed exercise programs (Huyser et al., 1997; Oliver et al., 2002; Dobkin et al., 2005; Dobkin et al., 2006; Dobkin et al., 2008). By reducing pain catastrophization it is believed that one could reduce fear-avoidance behaviours which are often displayed by patients with FMS and improve patient compliance toward exercise programs.

Empirical evidence suggests that cognitive-behavioural therapy (CBT), specifically exposure therapy, may be useful in the alteration of pain catastrophization observed in patients with FMS (Rodero et al., 2008). That imagined exposure therapy may effectively reduce pain catastrophizing in patients with FMS made the investigation of VRET a plausible treatment option for pain catastrophizing in FMS (Rodero et al., 2008). However, since there was no available virtual reality exposure therapy (VRET) program for the treatment of pain catastrophizing in patients with FMS at the time of this study; preliminary steps were required prior to the development and testing of such a program. Initially, it had to be ascertained if visual exposure to catastrophized exercise activities cognitively triggered the functional brain areas associated with pain catastrophizing in patients with FMS. The premise was that if visuals of the catastrophized exercise activities cognitively trigger pain catastrophizing in previously identified functional brain areas of patients with FMS (Gracely et al., 2004); a VRET exercise program aimed at exposing patients with FMS to visuals of the feared or catastrophized exercises and neutralizing feelings of catastrophization towards exercise activities, could possibly decrease pain catastrophizing and subsequently decrease fear of movement. In turn, compliance towards prescribed exercise programs may be increased.

5.1.2 Aim of this research

The overall aim of the research presented in the current thesis was to test a novel concept that exposing patients with FMS (who reported to catastrophize pain related to exercise), to visuals of healthy exercise activities elicits neurophysiological changes in functional brain areas associated with pain catastrophization. The research hypothesis was that if exposure to visuals of physical exercises/exertion elicited changes in functional brain areas associated with pain catastrophization; preliminary support (proof-of-concept) would be provided for the further development and testing of a specifically-designed VRET exercise program aimed at reducing pain catastrophization in patients with FMS.

5.1.3 Summary of research undertaken

Since this research was essentially proof-of-concept, various preparatory steps were initially required. A number of studies were therefore conducted, each significantly contributing to achieving the overall aim of this research.

Firstly, we reviewed the current available literature using a realist review methodology (Pawson et al., 2005) instead of a conventional systematic review methodology (chapter two). This approach proved to be ideal as a deeper and broader understanding of the literature underpinning the novelty of the concepts presented in this research was achieved (Pawson et al., 2005). Theoretical perspectives for this research were therefore derived, which were central in conceptualizing the ideas presented in this research.

Based on the results of chapter two, it was found that, like other developing countries, limited chronic pain epidemiologic information for South Africa exists (Walker et al., 2006; Chopra et al., 2008; Derman et al., 2011; Igumbor et al., 2011). In addition, the vast diversity present in South Africa, and the lack of adequate and valid outcome measures available for the South African population, makes conducting research among a South African population difficult (Derman et al., 2011; Igumbor et al., 2011). The second study (chapter three) of this

research therefore aimed to cross-culturally adapt and validate a number of outcome measures among patients with FMS living in the western parts of South Africa. A profile of this group was simultaneously established during this study. The cross-culturally adapted and validated outcome measures, namely the South African Pain Catastrophizing Scale (SA-PCS), the South African Tampa scale for kinesiophobia (SA-TSK) and the South African Revised Fibromyalgia Impact questionnaire (SA-FIQR) were utilized in the subsequent and final main study of this research (chapter four).

The main study of this research (chapter four) consisted of an interlinked three-phase study which primarily aimed to test a novel concept that exposing patients with FMS to visuals of healthy exercise activities elicits neurophysiological changes in functional brain areas associated with pain catastrophization. Each phase contributed to achieving the primary aim of this study. The *first* phase involved the development and validation of the fMRI visual task and consisted of four developmental steps. The *second* phase involved the exploration of the differences in neural correlates using fMRI, when patients with FMS and healthy controls (age, race, gender and socioeconomically matched) are exposed to various visuals of exercise and passive/relaxing activities. And the *third phase* involved the testing of the preliminary efficacy and feasibility of a provisionally-designed VRET exercise program on reducing pain catastrophization (subjectively measured using the SA-PCS; objectively measured using fMRI) in patients with FMS.

In the following chapter, the results (and interpretation thereof) of the individual studies conducted and presented in the preceding chapters (chapters two to four) will be reviewed, scrutinized and discussed. In addition, the implications of these study results for clinical practice, theory, the FMS patient, the healthcare professional, as well as the healthcare system will be discussed. Ultimately, an overall conclusion of this research will be provided. Limitations of this research will be highlighted and recommendations for future research will also be provided. *Please note that implications for and limitations of each individual study*

(presented in each chapter) will be discussed following discussion of that particular study's results for easier reference.

5.2 The South African FMS patient

Although it is acknowledged that chronic pain conditions, like FMS, are as common in the developing world as in the developed world (Peleg et al., 2008); accurate information about chronic pain epidemiology remains lacking for most developing areas, including South Africa (Walker et al., 2006; Chopra et al., 2008; Derman et al., 2011; Igumbor et al., 2011). In addition to the cross-cultural adaptation study presented in chapter three, a profile of the patients with FMS living in and around the Cape Metropole area of the Western Cape, South Africa, was also established. It was hoped that the information retrieved would enhance the understanding of the characteristics of FMS in a population living in and around the Cape Metropole area of the Western Cape (South Africa).

Ninety-three FMS subjects currently registered at the Tygerberg Hospital's (TBH) Rheumatology clinic participated in this study (chapter three). The subjects resided in and around the Cape Metropole area of the Western Cape, South Africa. It was not surprising that the majority of the subjects included in this study were female (n=89; 95.7%) (chapter three), which correlates with previous international studies (conducted in England, Spain and the USA), where it is reported that up to 95% of the study samples were female (Nelson et al., 2006; Rodero et al., 2008; Alda et al., 2011; Schaefer et al., 2011). These reported percentage values are consistent with the results of the literature review (chapter two) which report that FMS primarily affects more women than men by up to 1.67 times and that the male:female ratio for the prevalence of FMS is 1:9 (Bartels et al., 2009; Alabas et al., 2012). This over-representation of females in several chronic pain conditions, including FMS, has long been a topic of research (Lund et al., 2008; Bartels et al., 2009; Alabas et al., 2012). From the results of a number of studies conducted around the globe, it consistently appears that females are at greater risk of developing chronic pain compared to males (Lund et al.,

2008; Bartels et al., 2009; Alabas et al., 2012). Reasons for this greater risk in females are however not yet well known, but there are various theories which may explain this discrepancy in developing chronic pain conditions between the genders (Lund et al., 2008; Bartels et al., 2009; Alabas et al., 2012). According to Lund *et al.* (2008), it may be possible that interacting factors including genetic, hormonal, biological, environmental, sociocultural, psychological and behavioural elements may cause FMS to develop more in females than males. The gender difference in the development of chronic pain conditions may also partly be explained by the fact that the pressure pain test for tender points forms part of the diagnosis for FMS (Bartels et al., 2009). Some male patients with FMS may therefore remain unrecognized, since it is well known that males have a higher pain threshold than females (Bartels et al., 2009). A recent meta-analysis of six studies (406 men and 539 women) found a significant positive correlation between masculine and feminine personality traits and pain threshold and tolerance (Alabas et al., 2012). The study concluded that individuals who considered themselves more masculine and less sensitive to pain than the typical man showed higher pain thresholds and tolerances (Alabas et al., 2012). This finding may explain why fewer men than women are reportedly diagnosed with chronic pain conditions such as FMS. Other theories proposed for the gender differences in the developing of FMS have been the involvement of sex hormones in the pathophysiology of FMS (Okifuji et al., 2006). However, the study found that sex hormones seem to play a limited role in the development of FMS. Further research is therefore warranted to investigate the factors which contribute to the skewed gender distribution observed in the prevalence of FMS.

The mean±SD age of the subjects included in the current study was 47.28±10.38 years (chapter three). This finding was again not surprising, since the prevalence of FMS is known to be much higher in the middle-aged adult population than any other age group (Tsang et al., 2008; Assumpção et al., 2009). According to Carmona *et al.* (2001), the prevalence of FMS was estimated to be around 1.6% from age 30 to 39 years, and increased to 4.9% from age 40 to 49 years. However, the prevalence of FMS decreased to 3.7% from age 50 years

onwards (Carmona et al., 2001). In a comprehensive USA study, the mean±SD age of the FMS subjects included in the study was 47.9±10.9 years (Schaefer et al., 2011). In another USA study, the mean±SD age of the FMS study sample was reported to be 47±11 years (Reisine et al., 2008). Similarly, Nelson *et al.* (2006) reported a mean±SD age for a British FMS study sample of 47.4±13.5 years. The results of this study also concurred with a more recent and more local study, where it was reported that the majority of chronic pain sufferers in South Africa are women over the age of 40 years (Walker et al., 2006). The mean age of the sample included in this study was therefore comparable to other national and international FMS populations.

Of the included subjects, 73% were coloured, 41 % were black, 4 % were white and 2% were classified as “other” ethnicity, of which 44% were Afrikaans-speaking, 35% were English-speaking and 20% were Xhosa-speaking (chapter three). As expected, the language and ethnicity distribution of the profiled subjects correlated with the demographic statistics released by Statistics South Africa in the South African National Census of 2001 (SANC 2001) (StatsSA 2003). (The results of the SANC 2011 were not available to the public at the time of submitting this thesis). According to the SANC 2001, the Western Cape population comprises of 50.2% “coloured”; 30.1% “blacks”; 18.4% “whites” and 1.3% “India/Asian or other” (StatsSA., 2003). Afrikaans is the most predominant language spoken in the western parts of South Africa, with 55.3% of the Cape Metropole area population speaking Afrikaans as a first language (StatsSA., 2003). Xhosa is the first language of 23.7% and English, the first language of 19.3% of this population. In the “coloured” community, 81% speak Afrikaans as a first language; and in the “black” community 88.6% speak Xhosa as a first language. The “white” community is however evenly divided between Afrikaans- and English-speaking, at 55.4% and 43.2%, respectively (StatsSA., 2003). It can therefore be concluded that the sample included in this study was representative of the population currently residing in the Cape Metropole area of the Western Cape, South Africa, based on language and ethnicity.

The results of the current study indicated that 34.4% of the included subjects were married (chapter three). This result is however in contradiction with other international FMS population studies where it was found that a larger proportion of the included FMS subjects were married (Reisine et al., 2004; Nelson et al., 2006; Alda et al., 2011). Alda *et al.* (2011) reported that 67.3% to 71% of the included Spanish FMS subjects were married. Whereas Nelson *et al.* (2006) reported that 77% of the included British FMS subjects were married. In another FMS study conducted in the USA, it was reported that 59.6% of the included subjects were married (Reisine et al., 2004). A study conducted in 2003 investigated the impact FMS has on the spouse and the family (Söderberg et al., 2003). Although a small study (n=5), the findings of this qualitative study indicated that the wives' illness had a great impact on the husbands' lives and their role in the family with regards to workload and responsibility (Söderberg et al., 2003). The study also found that the husbands lacked information about the illness and that the entire family life was influenced (Söderberg et al., 2003). The presence of FMS therefore not only has an impact on the sufferer, but also influences the lives of the spouse and the family (Söderberg et al., 2003). Further research is however warranted in this area, since the impact of FMS on the spouse and the family should be taking into consideration when providing care for these patients.

The results of the profile study further indicated that 40.9% of the included subjects had a "lower than grade 12" (less than 12 years) education (chapter three). This information is however inconsistent with the results of a number of FMS studies where it was reported that a larger portion of FMS populations generally had lower levels of education (Walker et al., 2006; Peleg et al., 2008, Alda et al., 2011). In another South African study, it was found that approximately 73% of the chronic pain sample had an education level of 12 years and less (Walker et al., 2006). In a FMS study conducted in Spain, it was reported that of the included subjects, 40.4% to 50% had a primary school education, and 32.7% to 40.4% had a secondary school education (Alda et al., 2011). Peleg *et al.* (2008) however reported an even larger proportion (74%) of FMS subjects in Israel having a lower education level or no

education at all. Although not confirmed by any of these studies and neither by the current study, it has been previously postulated that the level of education of an individual may influence the impact of FMS and the health status of that person (Peleg et al., 2008). More research is however needed to confirm this allegation.

Of the included subjects in the current study, 34.4% were unemployed (chapter three). These results concurred with international USA studies which reported that nearly half of the included subjects (41%) were declared disabled, unemployed, or retired (Schaefer et al., 2011) and that 50% of the included subjects were employed (Reisine et al., 2008). The results of this study also concurred with the results reported by Alda *et al.* (2011), where up to 29.8% of the included population were unemployed. Interestingly, it has been reported that employment may provide a protective health benefit over time among FMS women (Reisine et al., 2008). According to Reisine *et al.* (2008), it has been shown that employed women are not only healthier, but that their health status declines at a much slower rate than when compared to FMS women who are unemployed. These findings suggest that it may be advantageous for FMS women to continue working as long as possible to retard the declination of their health (Reisine et al., 2008). However, in a country like South Africa, where the unemployment rate is high (up to 24.9% according to the Unemployment report/StatsSA 2012), one cannot simply suggest that patients with FMS return to work to increase or maintain their health. The exact reasons for the high unemployment rate reported among the sample included in the current study population was not established and therefore cannot be confirmed as being a direct result of developing FMS and its symptoms. Subjects included in this study may therefore have had other reasons for being unemployed, such as not being able to find a job, etc., and may not have voluntarily chosen to remain unemployed. Future studies should therefore establish the reasons for unemployment in larger FMS populations and appropriately address these issues.

The results of this study also indicated that 36.9% of the included subjects were current smokers. This result is however much higher than previously reported. In a study conducted by Lee *et al.* (2011), 9.8% out of 336 participants were current smokers. This study revealed that smoking habits may influence pain, functional and psychiatric features in patients with FMS (Lee et al., 2011). In another FMS study, it was found that 51 patients (21.9%) smoked (Yunus et al., 2002). The study reported a significantly positive relationship between smoking and pain, patient global severity, functional disability and numbness when age and education were adjusted for (Yunus et al., 2002). In addition, Weingarten *et al*. (2009) found that 14.7% of their study population were tobacco users. The study found that tobacco use was associated with greater pain intensity as measured by pain scales and the pain component of the Fibromyalgia Impact Questionnaire (FIQ) (Weingarten et al., 2009). Interestingly, it has been reported that the frequency of smoking in patients with FMS (77 subjects, 25.5%) tended to be higher than in Rheumatoid Arthritis (RA) patients (19 subjects, 16.5%) (p=0.05) (Pamuk et al., 2009). The study findings also indicated that current tobacco use was associated with more severe FMS symptoms in patients presenting to a specialized FMS treatment program (Pamuk et al., 2009). From the results of various epidemiologic studies, it can be deduced that smoking may have an influence on the disease manifestations or severity of FMS symptoms (Yunus et al., 2002; Weingarten et al., 2009; Pamuk et al., 2009; Lee et al., 2011). Although correlating smoking habits to FMS symptoms and subject characteristics was not an objective of the current study, the fact that the prevalence of smoking was found to be higher in this FMS population than previously reported for other FMS populations is reason for concern due the reported influence tobacco use may have on FMS symptoms. Future studies investigating the relationship between smoking and FMS among a larger South African population is therefore warranted.

The mean±SD pain catastrophization level, as measured using the SA-PCS, among the subjects included in the current study was 36.37±10.40. These results concurred with the results reported by Alda *et al.* in 2011, but were higher than the results reported by Nelson *et*

al. (2006) and Rodero *et al.* (2008). Alda *et al.* (2011) included three treatment groups and the baseline mean±SD pain catastrophization level as measured using the PCS was reported for each group. The mean±SD PCS scores ranged from 34.13±9.29 to 31.23±7.18 for the three groups, which is consistent with the mean±SD PCS scores reported in this study. However, Nelson *et al.* (2006) reported a mean±SD PCS score of 24.9±13.2 for the sample at baseline. Similarly, Rodero *et al.* (2008) reported a mean±SD PCS score of 25.33±3.54 for the eight subjects included in their study, which was lower than the mean PCS scores reported for this study. From the results of this study, it can be deduced that the levels of pain catastrophization among the South African FMS population may be similar, if not higher, than the prevalence of pain catastrophization reported for other FMS populations. We cannot be certain why the levels of pain catastrophization is reportedly higher in this group than previously reported, but we can assume that the sample sizes included in the previous studies could have attributed to the varying results reported. Nelson *et al.* (2006) and Rodero *et al.* (2008) included very small samples in their studies. This may have inadvertently contributed to the lower mean PCS scores among these groups. Nevertheless, the higher mean SA-PCS scores reported in this study supports the current literature that pain catastrophization is highly prevalent among FMS subjects (Hassett et al., 2000; Edwards et al., 2006). Future research is however warranted to ascertain if the prevalence of pain catastrophization is as high among South Africans living outside of the Western Cape area. In addition, it would be beneficial to ascertain if the prevalence and levels of pain catastrophization is as high in other chronic pain populations compared to FMS populations living in South Africa.

The relationship between pain catastrophization and fear-avoidance behaviours in chronic pain is well recognized (Vlaeyen et al., 2006). The high pain catastrophizing levels reported for this study sample was therefore expected to correlate with high kinesiophobia levels. Indeed, the results of the current study indicated that the mean±SD kinesiophobia (fear of movement/activity) level, as measured using the SA-TSK, among the included subjects was

reported as 50.80±6.52. This result concurs with the literature that prevalence of fear of pain and activity is reported as high (>37 points on the TSK) among patients with FMS (Turk et al., 2004). According to Turk *et al.* (2004), patients with high levels of fear of pain and activity reported greater disability, depressed mood, pain severity and treadmill use than patients with lower levels of fear. In a study by de Gier *et al.* (2003), high and low fearful patients with FMS (n=81) were requested to perform a physical task, a cognitive (reaction time) task, and a dual task in which the physical and cognitive tasks were combined. It was hypothesized that the high fearful patients would terminate the physical performance task sooner than low fearful patients, and would show a greater disruption on the cognitive task (de Gier et al., 2003). The results of the study showed that pain was a greater predictor of activity tolerance than pain-related fear, but that pain-related fear was the stronger predictor of reaction times on the cognitive task (de Gier et al., 2003). Based on the results of these previous studies, pain catastrophization and subsequent fear of movement (fear of pain and activity) is a significant concern for chronic pain sufferers since these behaviors result in the maintenance of chronic pain and increased disability (Turk et al., 2004). Pain catastrophization and patients' fears toward pain and activity/movement should therefore be addressed in the overall management of FMS (Turk et al., 2004). It is postulated that through this approach disability and rates of non-adherence and attrition from outcome studies and management programs could be reduced (Turk et al., 2004).

5.2.1 Implications for clinical practice and research

Although, it can be deduced from the results of this study that the South African FMS patient population is comparable to other international FMS patient groups; there are elements which were not similar and may be classified as unique to the South African FMS population.

For instance, the number of FMS subjects included in this study who smoked, was higher than previously reported. This is concerning since it has been established that smoking may influence the duration and severity of FMS-symptoms. Although further research is still

warranted in this area for the South African FMS population, it is recommended that clinicians currently involved in the management of FMS, should strongly advise patients with FMS to try and quit smoking.

Another finding of this study which warrants highlighting is the fact that pain catastrophization and kinesiophobia levels were found to be higher among the sample included in this study than previous reported. Reflecting the limited chronic pain epidemiologic information available for developing countries like South Africa (Derman et al., 2011; Igumbor et al., 2011), limited information regarding the prevalence of pain catastrophization and kinesiophobia in the South African FMS population, and other chronic pain populations, currently exists. As previously mentioned, pain catastrophization has shown associations with functional disability, pain severity, elevated disease activity and depression in chronic pain patients (Sullivan et al., 1995; Quartana et al., 2009; Engel-Yeger et al., 2011). Similarly, patients with FMS with high levels of fear of pain and activity (kinesiophobia) reported greater disability, depressed mood and pain severity than patients with lower levels of fear (Turk et al., 2004). Further research focusing on the area of pain catastrophization and fear-avoidance behaviours in the South African FMS and other chronic pain populations, is therefore warranted.

5.2.2 Limitations to this study

A limitation to this study was that the vast diversity present in South Africa, makes generalizing the results generated from this study to the rest of the country difficult. The study was limited to including subjects recruited from in and around the Cape Metropole area of the Western Cape, South Africa. Although the Cape Metropole constitutes a large portion of the South African population (StatsSA., 2003), it hardly includes the array of ethnic, cultural and language groups currently living in the rest of South Africa. Each province in South Africa is uniquely different from the other in terms of ethnicity, culture and language (StatsSA., 2003). For this reason, larger population studies including

representative samples from each province in South Africa is warranted. The sociodemographic information provided from this type of study would be more valuable than what is currently available.

In addition, with regards to the profile study presented in conjunction with the cross-cultural adaptation study in chapter three, it has to be admitted that by focusing on the main objective of cross-culturally adapting and validating the necessary outcome measures, less attention may have been paid to establishing a more detailed profile of the patient with FMS living in and around the Cape Metropole area of the Western Cape, South Africa. However, in our defense, we attempted to establish the basic sociodemographic profile of this study population and the results could be compared to other national and international studies. Larger, more detailed profile studies for the South African FMS patient are however warranted.

5.3 Cross cultural adaption of outcome measures for the South African FMS population

Populations and cultural sub-groups within populations across the globe, typically differ in language, dialect, lifestyle, morals, values, behaviour, customs, beliefs, perceptions of life and expression of disease (Guillemin et al., 1993; Gonzalez-Calvo et al., 1997; Beaton et al., 2000). The direct administration of existing and previously validated versions of self-report outcome measures in various countries, cultures and language groups, is therefore not always possible or advised. In these instances, misinterpretations of the questions/items or scoring systems, and culturally-inappropriate anchors or references, may compromise the integrity and validity of the responses that the outcome measure seeks (Guillemin et al., 1993; Beaton et al., 2000; Cook et al., 2006; Le Gal et al., 2010). The ramifications of utilizing linguistically- or culturally-inappropriate health outcome measures across various populations and cultures are therefore far-reaching; not only in terms of decisions made on effective care, but also in terms of health policies which may be developed from the research

findings. Accurate measurement across cultures is thus dependent on the linguistic and cultural adaptation and application of an outcome measure for a specific population (Beaton et al., 1998; Beaton et al., 2000; Cook et al., 2006; Le Gal et al., 2010).

For this reason, prior to conducting the main study of this research, the outcome measures which were to be used in the main studies, were cross-culturally adapted and validated among the current study population. Chapter three presents the methods and results of the study which was primarily aimed at cross-culturally adapting and validating the following outcome measures for use among a FMS patient population living in and around the Cape Metropole area of the Western Cape, South Africa: the PCS, TSK and FIQR. These measures, to our knowledge, were previously not validated among a South African population.

As anticipated, cross-cultural adaptation and validation of the PCS, TSK and FIQR for a South African sub-population was complex because of the cultural and linguistic variability evident in various areas of this uniquely diverse country. Although the outcome measures were cross-culturally adapted and validated in three of the most predominant languages (English, Afrikaans and Xhosa) of the Cape Metropole area (StatsSA., 2003); the translated and validated instruments resulting from this study may not be applicable to Zulu- or Sesotho-speaking patients with FMS living in the northern and eastern parts of South Africa (StatsSA., 2003). The instrument adaptations from this study may also not be applicable for, or accepted by, other English-, Afrikaans- and Xhosa-speaking groups living in the other parts of South Africa due to ethnic and cultural differences. Careful consideration for the diversity of the country is therefore required when applying any health outcome measure among various languages, cultural or ethnic groups uniquely found in South Africa. Further cross-cultural adaptation and validation of the SA-PCS, SA-TSK and SA-FIQR in other South African language and ethnic groups is therefore recommended. In other countries, the cross-cultural adaptation and validation of an outcome measure is typically reported for one

cultural/ethnic group in one predominant language. However, in a country like South Africa where vast diversity exists with regards to language, ethnicity, socioeconomics, culture and religion; the implementation of an outcome measure in one language is not possible. A total of 11 official languages are spoken throughout the country, with the dominance of each language varying between different parts of South Africa (http://www.sa-venues.com/sa_languages_and_culture.htm). The vast diversity present in South Africa should therefore always be considered when research is conducted among a South African population so that accurate measurements of outcomes are achieved and can be compared to other international reports.

Following the meticulous methodology described in chapter three, the South African versions of the PCS, TSK and FIQR were produced, namely the SA-PCS, SA-TSK and SA-FIQR. The following psychometric properties were evaluated for each adapted outcome measure: face and content validation, internal consistency, test-retest reliability, sensitivity-to-change and cross-sectional convergent validity. The results for the psychometric properties of each outcome measure will now be discussed.

5.3.1 Face and content validity

Face and content validation identified that the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR were acceptable, applicable and easily comprehended by the included subjects. The English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR were also simple to complete as it took subjects less than 5 minutes to complete each questionnaire. In South Africa, clinicians working in the public health sector particularly have limited time to consult with individual patients due to limited resources and staff (Varni et al., 2005). The time taken and the ease of completing a questionnaire, in addition to the cultural applicability of an outcome measure, therefore need to be considered. Accurate measurement is essential before, after and during all management programs for determining the progress of management and the effectiveness of a treatment. It is as important to ensure that acquiring these measures from patients is not frustrating for the

health professional and the patient and that clinicians do not neglect assessing outcomes on a regular basis due to time constraints (Varni et al., 2005). Furthermore, the adaptation and application of the scoring system of the South African versions of the PCS, TSK and FIQR proved to be easier for the subjects to understand. We anticipated that complicated scoring systems for outcome measures would be ineffective if the target group did not fully understand how the system worked, and how the system should be applied. As a result, incorrect responses and inaccurate study results and conclusions may have been obtained. The English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR can therefore be recommended as simple, efficient, easy-to-understand, easy-to-complete and valid tools to use among South African patients with FMS receiving services in the public health sector of the Cape Metropole area. Further validation is however required for application of the English, Afrikaans and Xhosa SA-PCS in public health sectors outside of the Cape Metropole area, the South African private sector and in future research studies.

5.3.2 Internal consistency

Internal consistency for the English, Afrikaans and Xhosa SA-PCS, as a whole, was found to be excellent (Cronbach's alpha (α) = 0.981, 0.984 and 0.970 respectively) in this study (chapter three). These estimates are higher than the original English PCS (α = 0.87) as well as the Spanish PCS (α = 0.79), Dutch PCS (α = 0.85), French PCS (α = 0.85); Singalese PCS (α = 0.89), Catalan PCS (α = 0.89); Italian (α = 0.92), Chinese PCS (α = 0.93) and German PCS (α = 0.94) (Sullivan et al., 1995; Monticone et al., 2011; Pallegama et al., 2009; Garcia-Campayo et al., 2008; Meyer et al., 2008; Miró et al., 2008; Yap et al., 2008; Tremblay et al., 2008; French et al., 2005; Crombez et al., 1999). However, the evaluation of internal consistency of the PCS as a whole is theoretically incorrect since, by definition, Cronbach's α "indicates the correlation among items that measure one single construct" (Osburn et al., 2000). The PCS contains three dimensions; hence evaluation of the internal consistency of each of the three subsections was required. The internal consistency for all subsections (*rumination, helplessness and magnification)* of the SA-PCS was also found to

be excellent and considerably higher than previously reported ICC's for subsections of the PCS. For instance, the high internal consistency for the subsection *magnification* of the English, Afrikaans and Xhosa SA-PCS (α = 0.961; 0.985 and 0.961, respectively) found in this study is contradictory to the majority of validation studies which have previously reported that internal consistency for the *magnification* subsection, in particular, is usually unsatisfactory (Sullivan et al., 1995; Monticone et al., 2011; Meyer et al., 2008; Miró et al., 2008; Tremblay et al., 2008; French et al., 20059). The internal consistency reported for the *magnification* subsection of the original English, French, French-Canadian, Catalan, Italian and German PCS ranged between α = 0.56 to 0.67 (Sullivan et al., 1995; Monticone et al., 2011; Meyer et al., 2008; Miró et al., 2008; Tremblay et al., 2008; French et al., 20059). It has been postulated that the low internal consistency found for the subsection *magnification* may relate to the few items contained in this subsection and that it should be reconsidered if this subsection can be reliably used as an independent instrument (Osburn et al., 2000). The higher internal consistency reported in this study may however be due to the fact that subjects took time to answer each question and may have considered each question more carefully, increasing the internal consistency for this subsection. The Chinese PCS reported an internal consistency of α = 0.768, for the subsection *magnification,* which was closest to that of this study (Yap et al., 2008). Further validation of the internal consistency of the English, Afrikaans and Xhosa SA-PCS among larger FMS sample groups in South Africa is however warranted.

Internal consistency for the English, Afrikaans and Xhosa SA-TSK as a whole, was found to be excellent (α = 0.940, 0.961 and 0.965, respectively) in this study (chapter three). The TSK was previously cross-culturally validated in a Norwegian sciatica population (Haugen et al., 2008), a Brazilian-Portuguese low back pain population (de Souza et al., 2008) and an Italian low back pain population (Monticone et al., 2010). The Cronbach's α's reported for the SA-TSK as a whole in this study, were higher than those reported for the Norwegian (α = 0.81), Brazilian-Portuguese (α = 0.082) and Italian TSK (0.772) (Haugen et al., 2008; de

Souze et al., 2008 and Monticone et al., 2010). The Cronbach's α's reported for the SA-TSK as a whole in this study, was also higher than the values reported for the original TSK (Goubert et al., 2004; Roelofs et al., 2004). Internal consistency was also analyzed for the two subsections of the SA-TSK, namely *Activity Avoidance (AA)* and *Somatic focus (SF)* (chapter three). For the subsection AA, the English, Afrikaans and Xhosa SA-TSK scored an α of 0.80, 0.85 and 0.82, respectively. For the subsection SF, the English, Afrikaans and Xhosa SA-TSK scored an α of 0.82, 0.76 and 0.82, respectively. These results were higher than the internal consistency reported for the subsections of the Italian TSK (Monticone et al., 2010). The Norwegian and Brazilian-Portuguese TSK however did not report on the internal consistency of the subsections of the TSK. Further validation of the internal consistency of the English, Afrikaans and Xhosa SA-TSK among larger FMS sample groups in South Africa is however warranted.

Internal consistency for the English, Afrikaans and Xhosa SA-FIQR as a whole, was found to be excellent (α = 0.946, 0.941 and 0.932, respectively) in this study (chapter three). The FIQR was previously cross-culturally validated in a Turkish FMS population (Ediz et al., 2011) and a Moroccan FMS population (Srifi et al., 2011). The Cronbach's α's reported for the SA-FIQR as a whole in this study, were slightly higher than those reported for the Turkish (α = 0.89) and Moroccan FIQR (α = 0.91) (Ediz et al., 2011; Srifi et al., 2011). In this study, internal consistency was also analyzed for the three subsections of the SA-FIQR, namely *Functional, Impact* and *Symptoms* (chapter three). For the subsection *Functional*, the English, Afrikaans and Xhosa SA-FIQR scored an α of 0.84, 0.81 and 0.79, respectively. For the subsection *Impact*, the English, Afrikaans and Xhosa SA-FIQR scored an α of 0.85, 0.85 and 0.84, respectively. For the subsection *Symptoms*, the English, Afrikaans and Xhosa SA-FIQR scored an α of 0.88, 0.86 and 0.83, respectively. However, internal consistency was not reported for the subsections of the Turkish and Moroccan FIQR, but rather each individual question and could thus not be compared. Further validation of the internal

consistency of the English, Afrikaans and Xhosa SA-FIQR among larger FMS sample groups in South Africa is however warranted.

It may be questioned why the internal consistency for the SA-PCS and SA-TSK especially were consistently much higher than their international counterparts. However, on the other hand, internal consistency for the SA-FIQR was only slightly higher than its international counterparts. One explanation for this may be that the SA-PCS and SA-TSK were compared to studies which included other chronic pain populations and not just FMS, whereas the FIQR is only applicable for patients with FMS. It may therefore be expected that the internal consistency results for the SA-PCS and SA-TSK may be different to those previously reported due to the variations in population disease groups. However, these points mentioned are but assumptions and further research is required to confirm these allegations.

5.3.3 Test-retest reliability

The SA-PCS showed excellent stability (test-retest reliability) as a whole with no significant differences between test and retest scores, for one month correlation: English SA-PCS (ICC = 0.904), Afrikaans SA-PCS (ICC = 0.908) and Xhosa SA-PCS (ICC = 0.891) (chapter three). These results were higher than the original English (ICC = 0.73), French (ICC = 0.73) and the Catalan versions (ICC = 0.76); were comparable to the Spanish (ICC = 0.84), German (ICC = 0.83), Italian (ICC = 0.842) and French-Canadian (ICC = 0.85) versions; but were lower than those reported for the Dutch (ICC = 0.92) and the Chinese (ICC = 0.96) versions of the PCS (Sullivan et al., 1995; Monticone et al., 2011; Garcia-Campayo et al., 2008; Meyer et al., 2008; Miró et al., 2008; Yap et al., 2008; Tremblay et al., 2008; French et al., 2005; Crombez et al., 1999). Excellent stability was also found for the subsections (*rumination, helplessness* and *magnification*) of each version of the SA-PCS with no significant differences between test and retest scores, which is analogous with previously reported ICCs for the subsections of the PCS (Sullivan et al., 1995; Monticone et al., 2011; Garcia-Campayo et al., 2008; Meyer et al., 2008; Miró et al., 2008; Yap et al., 2008;

Tremblay et al., 2008; French et al., 2005; Crombez et al., 1999). Further investigation into the test-retest reliability of the English, Afrikaans and Xhosa SA-PCS among larger FMS sample groups in South Africa is warranted.

The SA-TSK showed excellent stability (test-retest reliability) as a whole with no significant differences between test and retest scores, for one month correlation: English SA-TSK (ICC = 0.82), Afrikaans SA-TSK (ICC = 0.81) and Xhosa SA-TSK (ICC = 0.83). These results were lower than results reported for the Brazilian-Portuguese TSK (ICC = 0.93) and Italian TSK (ICC = 0.956) (de Souze et al., 2008; Monticone et al., 2010). Test-retest reliability was also analyzed for the two subsections of the SA-TSK, namely *AA* and *SF* (chapter three). For the subsection AA, the English, Afrikaans and Xhosa SA-TSK scored an ICC of 0.89, 0.933 and 0.929, respectively. For the subsection SF, the English, Afrikaans and Xhosa SA-TSK scored an ICC of 0.904, 0.933 and 0.919, respectively. These results were lower than the ICC's reported for the subsections of the Italian TSK (Monticone et al., 2010). ICC's for the subsections of the Brazilian-Portuguese TSK were not reported (de Souza et al., 2008). The Norwegian study however did not report ICC's for test-retest reliability, but rather a repeatability of eight according to Bland & Altmann (Haugen et al., 2008). Results between the Norwegian TSK and SA-TSK for test-retest reliability could therefore not be compared. Further investigation into the test-retest reliability of the English, Afrikaans and Xhosa SA-TSK among larger FMS sample groups in South Africa is therefore warranted.

The SA-FIQR showed excellent stability (test-retest reliability) as a whole with no significant differences between test and retest scores, for one month correlation: English SA-FIQR (ICC = 0.88), Afrikaans SA-FIQR (ICC = 0.87) and Xhosa SA-FIQR (ICC = 0.85). The ICC's reported for the SA-FIQR as a whole, were slightly higher than those reported for the Turkish (ICC = 0.835) and Moroccan FIQR (ICC = 0.84) (Ediz et al 2011; Srifi et al 2011). Test-retest was also analyzed for the three subsections of the SA-FIQR, namely *Functional, Impact* and *Symptoms* (chapter three). For the subsection *Functional*, the English, Afrikaans and Xhosa

SA-FIQR scored an ICC of 0.934, 0.925 and 0.922, respectively. For the subsection *Impact*, the English, Afrikaans and Xhosa SA-FIQR scored an ICC of 0.912, 0.904 and 0.891 respectively. For the subsection *Symptoms*, the English, Afrikaans and Xhosa SA-FIQR scored an ICC of 0.942, 0.934 and 0.912, respectively. However, ICC's were not reported for the subsections of the Turkish and Moroccan FIQR, but rather each individual question and could thus not be compared (Ediz et al 2011; Srifi et al 2011). Further investigation into the test-retest reliability of the English, Afrikaans and Xhosa SA-FIQR among larger FMS sample groups is therefore warranted.

The ICC values obtained for an outcome measure is however largely dependent on variance of disease patterns between subjects and it is acknowledged that the time period between the test and retest influences the size of this variance (DeVon et al., 2007; Lamé et al., 2008). The longer the time period between the test and retest, the more likely variance between subjects may occur and the lower the ICC value. Conversely, if the period between the test and retest is too short, there is a possibility that recall bias may occur, resulting in a higher test-retest correlation (DeVon et al., 2007). In chronic pain studies, there is also a good possibility that the results obtained will differ between individuals who are experiencing pain or symptoms at the time of the testing and those who are symptom-free (Lamé et al., 2008). According to Lamé *et al*. (2008), the latter group often responds to questions by trying to remember how they feel when they are actually experiencing pain or symptoms than what they are feeling at the time of measuring (Lamé et al., 2008). However, due to the chronicity of FMS, rapid changes in general health, pain/symptom patterns and disability are usually not expected, and the timing and experiences of pain and symptoms naturally vary. The period between the test and retest was therefore based on the usual clinical practice as suggested by DeVon *et al*. (2007) and Lamé *et al.* (2008). For instance in most outpatient public health facilities in South Africa, patients often have to wait a few weeks to months between treatments. Since the included FMS subjects were believed to not vary significantly in general health, pain/symptom patterns or disability within a short time period, the one

month period used between the test and retest was deemed appropriate to ascertain reproducibility of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR.

5.3.4 Sensitivity-to-change

Sensitivity-to-change was satisfactorily demonstrated in the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR. At a 95% confidence level, the minimal detectable change (MDC) of the English, Afrikaans and Xhosa SA-PCS, as a whole, indicated that a change of more than 8.84, 9.03 and 9.25 points after a given intervention, respectively, would not be due to measurement error. These values are however slightly lower than those reported for the Italian (10.45) and German PCS (12.8) (Monticone et al., 2011; Meyer et al., 2008).

At a 95% confidence level, the MDC of the English, Afrikaans and Xhosa SA-TSK, as a whole, indicated that a change of more than 7.76, 7.89 and 7.04 points after a given intervention, respectively, would not be due to measurement error. Sensitivity-to-change analyses were not reported for the Norwegian, Brazilian-Portuguese or Italian TSK (Haugen et al., 2008; de Souze et al., 2008 and Monticone et al., 2010) and could thus not be compared.

At a 95% confidence level, the MDC of the English, Afrikaans and Xhosa SA-FIQR, as a whole, indicated that a change of more than 21.15, 21.76 and 21.59 points after a given intervention, respectively, would not be due to measurement error. Sensitivity-to-change analyses were not reported for the Turkish and Moroccan FIQR and could thus not be compared (Ediz et al., 2011; Srifi et al., 2011).

5.3.5 Cross-sectional convergent validity

The scores of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR were correlated to the scores of pain severity (5-point Likert scale) and each other. Significant correlations ($p<0.05$) were found between the English SA-PCS and SA-TSK ($p = 0.011$),

Afrikaans SA-PSC and SA-TSK (p = 0.004) and Xhosa SA-PCS and SA-TSK (p = 0.038); as well as between the Afrikaans SA-PCS and SA-FIQR (p = 0.049) and the Afrikaans SA-TSK and SA-FIQR (p = 0.01). The results of this study show that the SA-PCS related with pain severity, fear-avoidance behaviours and impact of FMS in an expected manner, and vice versa. However, the results for the cross-sectional convergent validity of the SA-PCS in relation to the SA-TSK and SA-FIQR, and vice versa, in this study should therefore be viewed with caution, since the SA-TSK and SA-FIQR were validated at the same time as the SA-PCS. Further research is therefore warranted to establish the cross-sectional convergent validity of the SA-PCS, SA-TSK and SA-FIQR among a larger South African FMS sample.

5.3.6 Implications for clinical practice and future research

The current study findings indicated that the cross-culturally adapted English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR showed good face and content validity, excellent internal consistency, excellent test-retest reliability; as well as satisfactory sensitivity-to-change and cross-sectional convergent validity. The SA-PCS, SA-TSK and SA-FIQR can therefore be recommended as simple, efficient, valid and reliable tools for use among English, Afrikaans and Xhosa-speaking patients with FMS attending the public health sector in the Cape Metropole area of the Western Cape, South Africa. Due to the vast diversity in language, culture and ethnicity evident in South Africa, additional cross-cultural adaptation and validation of the SA-PCS, SA-TSK and SA-FIQR is required for application in FMS and chronic pain populations living in other provinces of South Africa. Further testing of the psychometric properties of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR in larger study samples is however warranted to confirm recommendations regarding its use in future research studies.

5.3.7 Limitations to this study

It is acknowledged that a major limitation to this study was that the SA-PCS, SA-TSK and SA-FIQR should have been correlated with a ‘gold standard’. However, to our knowledge,

since no such measures currently exists for pain catastrophization, kinesiophobia and impact of FMS, the SA-PCS, SA-TSK and SA-FIQR were correlated with related outcome measures such as each other and pain severity, to establish cross-sectional convergent validity (Engel-Yeger et al., 2011). However, the cross-cultural adaptation and validation of the SA-PCS, SA-TSK and SA-FIQR for a South African FMS population was concurrently conducted. Although, it was decided that for this study it would be appropriate to correlate the scores of the English, Afrikaans and Xhosa SA-PCS, SA-TSK and SA-FIQR to each other, we anticipate criticism regarding this decision. Furthermore, it may be criticized why the SA-PCS, SA-TSK and SA-FIQR were not correlated with intensity of pain/symptoms, such as the Numerical Rating Scale or the Visual Analogue Scale, which are widely-accepted and valid outcome measures. Instead, in the current study severity of pain/symptoms was measured and subjects were required to report on the everyday activities which increased their pain and symptoms. To defend our research approach, at the time of conceptualizing the study, it was understood that in chronic pain patients, severity of pain and symptoms, and activities which increase pain and symptoms, are of more use as this potentially reflects the patients' perceptions of his/her conditions, rather than quantifies pain and symptoms which may not always be present or present at the time of testing. Scores obtained from the SA-PCS, SA-TSK and SA-FIQR could therefore be related to the severity of the subject's pain and symptoms. The relationship between catastrophization, avoidance of a particular activity and the influence FMS has on an individual's life, may therefore be more naturally determined than based on momentarily-experienced symptoms.

Another limitation to this study was that the SA-PCS, SA-TSK and SA-FIQR were validated among English, Afrikaans and Xhosa-speaking patients with FMS living in and around the Cape Metropole area of the Western Cape, South Africa and not the entire South Africa. For this reason, the current validated SA-PCS, SA-TSK and SA-FIQR may not be applicable for administration among patients with FMS residing in other parts of South Africa due to the vast differences in ethnicity, cultures and languages between various provinces of South

Africa. Further cultural and linguistic validation of the SA-PCS, SA-TSK and SA-FIQR for other areas of South Africa is therefore required. In addition, the sample sizes for each language group, *viz.* the English, Afrikaans and Xhosa language groups, were small, and larger studies are required to further validate the SA-PCS, SA-TSK and SA-FIQR for the FMS population living in various parts of South Africa.

Factor analysis was not performed in this study and may also be deemed as a limitation. However, according to DeCoster (1998), the objectives for doing exploratory and confirmatory analysis may not actually have applied to this study. Basically, exploratory factor analysis should be used when one is interested in making statements about the factors that are responsible for a set of observed responses (DeCoster., 1998). The primary objectives of an exploratory factor analysis are to determine: 1) the number of common factors influencing a set of measures; and 2) the strength of the relationship between each factor and each observed measure. Some common uses of exploratory factor analysis are to: 1) identify the nature of the constructs underlying responses in a specific content area; 2) determine what sets of items “hang together" in a questionnaire; and to 3) demonstrate the dimensionality of a measurement scale (DeCoster., 1998). Researchers often wish to develop scales that respond to a single characteristic; determine what features are most important when classifying a group of items; and generate\factor scores representing values of the underlying constructs for use in other analyses. Since this was not the case in this study, exploratory factor analysis was not conducted (DeCoster., 1998). On the other hand, confirmatory factor analysis should be used when one has large numbers of data (DeCoster., 1998). The primary objective of a confirmatory factor analysis is to determine the ability of a pre-determined factor model to an observed set of data (DeCoster., 1998). Some common uses of confirmatory factor analysis are to: 1) establish the validity of a single factor model; 2) compare the ability of two different models to account for the same set of data; 3) test the significance of a specific factor loading; 4) test the relationship between two or more factor loadings; and 5) test whether a set of factors are correlated or uncorrelated

(DeCoster., 1998). Since items were not added or removed from the adapted outcome measures in this study, the factors within the outcome measures were believed to essentially remain the same, hence factor analysis (neither exploratory nor confirmatory) was not deemed necessary in this study.

5.4 Exploration into the functional imaging of catastrophization in FMS subjects

Chapter four presents the methods and results of an interlinked three-phase exploratory study which was central in testing the novel concept that exposing patients with FMS to visuals of exercise activities elicits neurophysiological changes in functional brain areas associated with pain catastrophization, and not in healthy controls. The *first* phase involved the development and validation of the fMRI visual task and consisted of four steps, each significantly contributing to the development of the final fMRI task for this study. The *second* phase involved the exploration of the differences in neural correlates using fMRI, which occur between patients with FMS and healthy controls (age, race, gender and socioeconomically matched), when these groups are exposed to various visuals of exercise and passive/relaxing activities. The *third* phase involved the testing of the preliminary efficacy and feasibility of a provisionally-designed VRET exercise program on reducing pain catastrophization (subjectively measured using the SA-PCS; objectively measured using fMRI) in patients with FMS. The results (and interpretation thereof) for each phase of this study will now be discussed.

5.4.1 The development and validation of the fMRI task (phase 1)

The development and validation of the visual tasks used during the fMRI scans in the main phases of this study (phases two and three; chapter four) was an important part of this study and required meticulous planning. A number of developmental steps were therefore followed to ensure that the final fMRI visual task developed would incorporate the most appropriate visual tasks to elicit the construct of interest (*viz.* pain catastrophization) in the functional

brain areas of patients with FMS (and healthy controls) during the fMRI scanning procedures (phases two and three; chapter four).

Firstly, an initial set of visual tasks had to be selected as stimuli for the fMRI task (chapter four; phase one; step one), which turned out to be quite difficult. This was, however, anticipated since selecting optimal tasks to best elicit the construct of interest in any fMRI study is hardly straightforward (Niskanen et al., 2012). The main aim of selecting tasks for any fMRI study is to reduce the chances of subjects reacting unexpectedly towards the stimuli and eliciting unwanted constructs. Many unusual factors had to therefore be considered prior to selecting visuals for the fMRI task for this particular group of subjects.

Besides being known for its vast diversity and rich culture, South Africa is also well-known for its high incidence of crime, domestic violence and drug abuse (http://www.uact.org.za/statistics; Nyabadza et al., 2010; Rashe., 2008). These political and social issues may have been deemed irrelevant for most other population groups, but ignoring them for the South African population could have had confounding effects. At this initial stage, we therefore attempted to the best of our ability, to reduce the elicitation of unwanted constructs to certain visuals as we anticipated that many of the subjects included in this study may have been in some way or the other affected by either crime, domestic violence or drug abuse. For instance, due to the high usage of drugs among the youth living in the Western Cape of South Africa (Nyabadza et al., 2010), we anticipated that many subjects who were included in this study may have had a child who was currently abusing drugs. To avoid eliciting emotions other than the construct of interest (*viz.* pain catastrophization), such as depression, anger or sadness some subjects may have been harbouring toward their children; all visuals of activities depicting children or mothers with their children were discarded. Similarly, there is a high incidence of domestic violence among families living in the Western Cape, which is especially directed towards the women of the household (Rashe., 2008). For this reason it was thought that any visuals depicting

couples and families may have inadvertently affected those female subjects who had previously or were currently experiencing domestic violence in their homes, or who were unhappy in their homes due to certain circumstances. Visuals of activities depicting couples and families were therefore discarded to avoid the elicitation of unwanted constructs among the included subjects. Although there may have been other factors we did not consider during the initial stage of selecting the fMRI tasks, we are confident that by eliminating elements such as children, couples and families from the visuals, we avoided (to the best of our ability) unnecessary and unwanted reactions or elicitations from subjects.

The second step in developing the fMRI task for this study involved conducting a pilot study (chapter four; phase one; step two). The pilot subject recruited for the pilot study was a 40-year-old divorced mother of three, living in the Cape Metropole area, with a four-year history of FMS. Based on the sociodemographic information of the pilot subject, we were confident that the pilot subject was representative of the FMS population group which were later included in this study. During the first pilot study, the logistics of the fMRI scanning procedure, the task duration and the presentation of the visual tasks were tested. Unexpectedly however, the pilot subject highlighted a few aspects of the fMRI task which initially we had not considered. For instance, the pilot subject did not like the fact that the visuals were black and white, and not in colour. When we initially converted the visuals from colour to black and white, we assumed that additional colour in the visuals would distract the subjects from the activity being depicted in the visual. The pilot subject however felt differently, and requested that the colour in the visuals be retained, since it became “boring” or monotonous to view black and white visuals over a period of time, which was in retrospect a logical request. In a number of studies which provide guidelines on designing fMRI studies, it is mentioned that the fMRI task should not be monotonous, but keep the subject interested for the duration of the task (Amaro et al., 2006; Niskanen et al., 2012). The pilot subject also highlighted the fact that she could not relate to visuals depicting much older women (over 70 or 80 years old). Considering that the prevalence of FMS is higher among middle-aged

women than any other age population (Carmona et al., 2001), again in retrospect, we should have considered this factor when selecting the initial visuals for the fMRI task. Lastly, the subject indicated that there was a particular visual which made her feel depressed or sad. The visual she was referring to was one in which a woman was sitting with her back facing the camera and looking over the ocean. Initially, it was thought that the visual was quite relaxing, but we never considered the fact that it may have evoked feelings of depression or even suicide in patients with FMS who may have been more vulnerable. Overall, the first pilot study was extremely useful and revealed many aspects which we had not considered which required modification prior to further development of the fMRI task for use in the rest of the study.

Following modifications of the visuals, further validation of the visual tasks was conducted among a small group of FMS subjects (focus group study; chapter four; phase one; step three). Again, the focus group session revealed aspects of the task which we had not considered and which required modification. One of the most unexpected revelations from the focus group session was that one of the active visuals depicting a woman skipping, actually evoked feelings of happiness rather than pain. We never considered the fact that subjects may have related the skipping activity depicted in the visual to their childhood days which elicited happy feelings instead of painful ones. Another visual depicting a woman napping was also found to evoke unexpected feelings in the FMS focus group. Instead of eliciting feelings of relaxation as we initially thought, it evoked feelings of sadness and depression. In retrospect, this unusual reaction from some of the subjects in the focus group was actually logical. One of the most prevalent FMS symptoms reported are sleep disorders (Shillam et al., 2011), and when exposed to visuals of someone napping, some subjects in the FMS focus group may have related the napping activity to their sleeping disorders, and the fact that they have trouble sleeping at night due to their FMS. Napping was therefore not seen as a relaxing event but rather a troublesome one. Overall, the focus group session was

useful in further validating the fMRI task, and like the first pilot study revealed aspects of the task which required modification prior to developing the final fMRI visual task.

Based on the results of the first pilot study and the focus group study, the final fMRI visual task was produced, and used during the fMRI scan procedure of pilot study two (chapter four, phase one, step four). The data acquired for pilot study two were analyzed accordingly. The main aim of the second pilot study was to ascertain if the developed fMRI visual task elicited the expected functional brain areas; i.e. the visual cortex and the functional areas which have previously been reported to be associated with pain catastrophization (Gracely et al., 2004).

To reiterate (from chapter four), four blood oxygenation level dependent (BOLD) contrasts were acquired during the fMRI scans for the subject during the following conditions: 1) *active>rest* condition (where brain activations during the rest period were subtracted from the active condition); 2) *passive>rest* condition (where the brain activations during the rest period were subtracted from the passive condition); 3) *active>passive* condition (where the brain activations during the passive condition were subtracted from the active condition); and 4) *passive>active* condition (where the brain activations during the active condition were subtracted from the passive condition). For these analyses, fMRI data acquired during the active>rest and passive>rest conditions, as well as the active>passive and passive>active conditions were of interest and were analyzed for the pilot subject as the main aim of the analyses at this stage was to ascertain if the pre-processing, analyses and output of the data were accurate.

From the results of the second pilot study, it was found that during the active>rest and passive>rest conditions, the expected functional areas which are well-acknowledged as being associated with vision, *viz.* the visual cortex situated in the occipital lobe (Bear et al., 2001; pg 313) were significantly activated (p<0.0000). The elicitation of the visual cortex

during both the active>rest and passive>rest conditions (chapter four), suggested that the analyses of the data and the output of the analyses were accurate, to our knowledge.

Significant activation of the *right inferior frontal gyrus* (p<0.0000) was found for the pilot subject during the active>passive condition (where the brain activations for the passive condition were subtracted from the active condition). These results concurred with a study conducted by Gracely *et al.* (2004) who examined the association between catastrophization and the brain's responses to a blunt pressure stimulus using fMRI among 29 FMS subjects. The FMS subjects were divided into those who were high catastrophizers and those who were low catastrophizers (Gracely et al., 2004). Differences in neural correlates were elucidated between the two groups of subjects. Among other functional areas significantly activated, Gracely *et al.* (2004) found that activity in the inferior frontal gyrus was associated with pain catastrophization in the high catastrophizing FMS patient group. Activation of the right inferior frontal gyrus during the active>passive condition for the pilot subject may therefore have provided preliminary proof that the construct of interest *viz.* pain catastrophization was elicited by the chosen fMRI task.

During the active>passive condition, the *right insular cortex* was also significantly activated for the pilot subject (p<0.0000). This result again concurred with the results of a study conducted by Gracely *et al.* (2004). Gracely *et al.* (2004) reported that activation in the insular cortex may be associated with pain catastrophization in high catastrophizing patients with FMS. However, Gracely *et al.* (2004) also reports that the contralateral insular cortex were associated with pain catastrophization in high catastrophizing patients with FMS. But in this study, only the right insular cortex was found to be significantly activated during the active>passive condition for the pilot subject. Although not conclusive, this difference in activation may be due to the fact that different stimuli were used in the two studies which may have possibly activated functional areas differently. Nonetheless, the activation of the insular cortex for the pilot subject during the active>passive condition, once more may have

provided preliminary proof that the fMRI task developed for this research study may have elicited the construct of interest *viz.* pain catastrophization.

The pilot data further revealed significant activation ($p<0.0000$) in the *right posterior cerebellum* during the active>passive condition. The cerebellum is a region of the brain that plays an important role in motor control, but may also be involved in some cognitive functions such as attention and language, and affective regulation such as regulating of fear and pleasure responses (Baillieux et al., 2008, Stoodley et al., 2010). The finding of significant activation in the posterior cerebellum for the pilot subject when exposed to visuals of exercises compared to visuals of passive/relaxed activities is analogous to the finding of Gracely *et al.* (2004) who reported that the activation in the cerebellum was associated with pain catastrophization in high catastrophizing patients with FMS. Gracely *et al.* (2004) however reported that both the anterior and posterior cerebellum were involved, where only the posterior cerebellum was found to be significantly activated in this pilot study during the active>passive condition. Nonetheless, activation of the posterior cerebellum during the active>passive condition for the pilot subject may have provided further preliminary proof that the construct of interest *viz.* pain catastrophization was elicited by the chosen fMRI task.

The analyses of the data for the pilot subject also revealed significant activation of the *right amygdala,* a group of nuclei located deep within the medial temporal lobes of the brain, which are associated with the processing of memory and emotional reactions such as fear (Bear et al., 2001; pg 588; Sergerie et al., 2008), during the active>passive condition. Although the amygdala was not specifically reported by Gracely *et al.* (2004) to be associated with pain catastrophization, it was however mentioned that the claustrum, an area closely connected to the amygdala, was found to be associated with the emotional aspects of pain (Gracely et al., 2004). Furthermore, the amygdala has also been reported to be associated with processing of visual social stimuli and to play a role in social cognition (Adolphs et al., 2006). When reflecting on the current known and reported functions of the

amygdala, activation of the amygdala during the active condition of the fMRI task used in this study may be logical. Simply stated, while the subject was exposed to the visuals of exercise activities during the fMRI scan, the subject may have processed the visual as being a social event, may have had a memory of doing a similar activity, and may then have experienced fear towards that particular activity, resulting in activation of the amygdala during the active>passive condition of this study (Adolphs et al., 2006). Further research is however warranted to confirm the involvement of the amygdala in the processing of pain catastrophization among patients with FMS when exposed to painful or non-painful stimuli, as we cannot be certain this was the case.

Interestingly, the *right thalamus* was found to be activated during both the active>passive and passive>active condition for the pilot subject. The main function of the thalamus, a midline symmetrical structure situated between the cerebral cortex and midbrain, is to relay sensory and motor signals to the cerebral cortex, along with the regulation of consciousness, sleep, and alertness (Burgmer et al., 2009). The thalamus is also believed to play a role in processing emotions, motivation, mood, sense of pain and pleasure, survival instincts and reproduction (Bear et al., 2001; pg 427). These functions reported for the thalamus may explain activation of the thalamus during both conditions since sensory input from the visuals were relayed to the brain in both conditions, and not just during one condition. Subjects were subjected to visuals of active and passive activities, and may have related certain emotions or feelings to the various visuals. Further research is however warranted to establish the role of the thalamus when an individual is exposed to visuals of exercise activities and passive activities.

In conclusion, from the findings of the final pilot study, it can be deduced that the fMRI task developed elicited the expected functional brain areas, namely the visual cortex (during both conditions) and areas previously found to be associated with pain catastrophization, namely, the right inferior frontal gyrus, the right insular cortex, and the right posterior cerebellum

during the active>passive condition. Additional, however, the right amygdala was found to be significantly activated during the active>passive condition. Pilot study two may therefore have provided sufficient preliminary proof that the fMRI task developed during phase one of this study was appropriate for use in the subsequent phases of this study (phases two and three) since the construct of interest, *viz.* pain catastrophization was elicited in a patient with FMS.

5.4.2 Differences in neural correlates associated with pain catastrophization between patients with FMS and healthy controls

Chapter four further presents the methods and results of phase two of the main study, an fMRI exploratory study aimed at elucidating the differences in neural correlates using fMRI, occurring between patients with FMS and healthy controls when these groups are exposed to various visuals of exercise and passive/relaxing activities. A total of 13 FMS subjects and nine healthy matched controls participated in this phase of the study. The FMS subjects and healthy controls were matched according to age, gender, ethnicity and socioeconomic status. There was no significant difference between the two study groups in age (p=0.34) (chapter four). However, the number of hours spent on physical activity per week as measured using the GPPAQ, significantly differed between the FMS subject group and the control group (p<0.0000) (chapter four). The latter finding could however have been expected, as the control group were healthy individuals and would most likely have participated in more physical activity than the FMS subject group. In addition, more of the healthy subjects than the FMS subjects were permanently employed (chapter four), which may have contributed to their average reported hours of physical activity per week.

The mean differences in functional brain activation during the active>rest, passive>rest, active>passive and passive>active conditions between the FMS subjects and the healthy controls at baseline were analyzed. Again, the condition of interest was the active>passive

condition, since it was thought that significant activation during this condition would signify association with the construct of interest *viz.* pain catastrophization, the most.

The FMS subject group showed significant activation in the *right inferior frontal gyrus* (p<0.0000) (chapter four) during the active>passive condition when compared to the healthy controls. Similarly to the second pilot study, these results concur with the study conducted by Gracely *et al.* (2004) who found that activity in the inferior frontal gyrus was associated with pain catastrophization in the high catastrophizing patients with FMS (Gracely et al., 2004). More recently however, studies have examined the role of the inferior frontal cortex in belief-bias reasoning and deductive reasoning tasks using repetitive transcranial magnetic stimulation (rTMS) (Tsujii et al., 2010; Tsujii et al., 2011). The studies found that the inferior frontal gyrus may play a significant role in belief-bias reasoning and deductive reasoning tasks (Tsujii et al., 2010; Tsujii et al., 2011). Belief-bias is currently defined as the tendency of an individual to be "erroneously biased when logical conclusions are incongruent with belief about the world" (Tsujii et al., 2010). Although belief-bias reasoning holds a different definition to that of pain catastrophizing, the significant activation of the right inferior frontal gyrus for the FMS subjects, and not the controls, during the active>passive condition of this study implies that there may have been a tendency for the FMS subjects to have a belief-bias reasoning reaction toward the exercise activities, similarly to a catastrophization reaction. Although the study conducted by Gracely *et al.* (2004) differed considerably from the current study in terms of the stimuli used during the fMRI task; the fact that the right inferior frontal gyrus was exclusively or significantly activated in the FMS subjects may however provide further support for the involvement of the right inferior frontal gyrus in pain catastrophization and belief-bias reasoning toward non-painful stimuli. Further research is however required to ascertain the exact involvement of the right inferior frontal gyrus in pain catastrophization and belief-bias reasoning in patients with FMS.

Right posterior cerebellum activation was significant (p<0.000) (chapter four) for the FMS subject group during the active>passive condition when compared to the healthy controls. As mentioned in the second pilot study, the cerebellum plays an important role in motor control, but may also be involved in some cognitive functions such as attention and language, and affective regulation such as regulating of fear and pleasure responses (Baillieux et al., 2008, Stoodley et al., 2010). Previously it has also been reported that viewing of emotional images from the International Affective Picture Scale (IAPS) (Lang et al., 2005 cited in Stoodley et al., 2010) activates the posterior lobe of the cerebellum when compared to viewing neutral images. Activation of the cerebellum was also seen in neuroimaging studies investigating panic, as well as sadness and grief (Stoodley et al., 2010). The posterior cerebellum has also been found to activate during painful stimulation, but more specifically during the anticipation of pain (Ploghaus et al., 1999 cited in Gracely et al., 2004). Furthermore reports have found that the posterior cerebellar regions are involved when processing one's own painful experience (Stoodley et al., 2010) and may be associated with pain catastrophization in high catastrophizing patients with FMS (Gracely et al., 2004). The functions currently reported for the posterior cerebellum can possibly explain the significant activation of the posterior cerebellum for the FMS subject group in this study when the subjects were exposed to visuals of exercise activities during the active>passive condition. Although we cannot be certain if the activation of the posterior cerebellum was exclusively associated with pain catastrophization toward the exercise activities depicted in the active visuals, we cannot for certain discard this finding. Regardless, the posterior cerebellum is also reportedly involved in a variety of emotional processes such as fear (Baillieux et al., 2008, Stoodley et al., 2010), and this involvement may explain the activation of this area during the active>passive condition of this study for the FMS subject group, and not the control group. The FMS subject group may have experienced feelings of fear, if not catastrophization, toward the visuals depicting the exercise activities. Further research is however warranted to confirm the involvement of the posterior cerebellum in the processing of pain catastrophization and fear toward exercise activities in patients with FMS.

Significant activation ($p<0.0000$) in the *right middle frontal gyrus* was found for the FMS subject group during the active>passive condition (chapter four). The middle frontal gyrus is involved in high-level executive functions and decision-related processes such as cognitive control, working memory, semantic processing, target detection, memory retrieval, recognition, prospective memory and processing of emotional stimuli (Talati et al., 2005). In addition, it has also been reported that the middle frontal gyrus may be associated with pain catastrophization in high catastrophizing patients with FMS (Gracely et al., 2004). These functions reported for the middle frontal gyrus may explain activation of this area for the FMS subject group during the active condition (where the brain activations for the passive condition were subtracted from the active condition). The FMS group would have most probably seen the active visuals (visuals depicting exercise activities), recognized what the visual was depicting (recognition), retrieved a memory related to that particular activity depicted in the visual (memory retrieval), and then either processed an emotion towards that particular activity depicted in the visual (processing of emotional stimuli) or may have thought of what they would feel if they did the activity (prospective memory), and may even have catastrophized toward the exercise activities. Although this reaction to the active visuals cannot be stated for certain, it does provide a logical explanation for the activation of the middle frontal gyrus in the intervention group during the active>passive condition in this study. Further research is however warranted to investigate the role of the middle frontal gyrus in processing emotions and constructs such as pain catastrophization toward exercise activities in patients with FMS.

Significant activation of the *left thalamus* was also found for the FMS subject group during the active>passive condition when compared to the healthy control group. In phase one, the pilot subject should activation in the right thalamus. However, in phase two, activation was only found for the left thalamus in the FMS subject group. To reiterate, the reported functions for the thalamus include the processing of emotions, motivation, mood and sense of pain and pleasure (Bear et al., 2001; pg 427; Burgmer et al., 2009). Despite the differences in

hemispheres, the fact that activation of the thalamus exclusively occurred for the FMS subject group and not the healthy controls, and then also for the pilot subject who suffered from FMS, may indicate that the thalamus plays a role in the processing of various stimuli in patients with FMS differently to healthy individuals. Further research is however warranted to confirm this finding.

In conclusion, the exclusive activation of the *right inferior frontal gyrus*, *right posterior cerebellum,* and *middle frontal gyrus* in the FMS subject group during the active>passive condition may not provide conclusive evidence, but does provide preliminary support for the hypothesis of this study. To reiterate, the main hypothesis of this study was that exposure to visuals of exercise activities would elicit functional areas associated with pain catastrophization in patients with FMS, and not healthy controls. Fundamentally, the concept of a novel VRET exercise program for pain catastrophization in patients with FMS would be proven. The inferior frontal gyrus, posterior cerebellum and middle frontal gyrus have been previously associated with pain catastrophization in patients with FMS (Gracely et al., 2004), which may indicate that FMS subjects in this study catastrophized the active visuals (visuals depicting the exercise activities) and not the passive visuals (visuals depicting the relaxing activities). It however cannot be stated for certain if the inferior frontal gyrus, posterior cerebellum and middle frontal gyrus were solely associated with pain catastrophization in the patients with FMS, or if activation of these areas were due to one of their other reported functions. Nonetheless, based on the findings of this phase of the study, it can be suggested (though not conclusively) that preliminary support was provided for the testing of a novel VRET exercise program as a treatment for pain catastrophization in patients with FMS (phase three). It is however recommended that further research be conducted to investigate the roles of the inferior frontal gyrus, posterior cerebellum and the middle frontal gyrus, as well as the amygdala and thalamus, in processing pain catastrophization toward exercise activities. In addition, it would be worthwhile to extend the sample size of this study to ensure that findings of significant brain activations were not confounded by small sample sizes.

5.4.3 Preliminary efficacy of a VRET for pain catastrophization

The final phase of the study presented in chapter four was aimed at testing the preliminary efficacy and feasibility of a novel VRET exercise program as a treatment for pain catastrophization among patients with FMS. (Preliminary support (though not conclusive evidence) for this concept was provided by the findings of phase two of this study). Twelve FMS subjects (retained from phase two of this study) were allocated to either the intervention group (VRET group) or the control group (waiting list group). There were no significant differences ($p>0.05$) in age; the number of hours spent on physical activity per week; the number of years living with FMS; SA-PCS scores; SA-TSK scores and SA-FIQR scores between the two study groups (chapter four) at baseline.

Outcomes, namely the SA-PCS and SA-TSK, were measured at baseline (pre-intervention) and post-intervention for both the intervention and control groups (chapter four). No significant differences (*$p>0.05$)* between the two groups for subjective PCS and TSK scores at baseline neither at post-intervention (chapter four) were found, although the mean differences between the baseline and post-intervention SA-PCS and SA-TSK scores for the VRET group were slightly higher than for the control group. This insignificant finding may however be due to the small sample size included in this study. Future studies should therefore include larger samples to detect significantly different results.

To ascertain the preliminary efficacy of the novel VRET program as a treatment for pain catastrophization in patients with FMS, differences in mean activation of functional brain areas during the active>passive and passive>active conditions between the two groups at baseline and post-intervention were compared. Again, the condition of interest was the active>passive condition, since significant activations during this condition was believed to signify association with the construct of interest *viz.* pain catastrophization.

5.4.3.1 Baseline between group comparisons

At baseline, during the active>passive conditions, the intervention group showed significant activation (p<0.0000) in the *right insular cortex, right anterior and posterior cerebellum, the right parahippocampal gyrus, right middle frontal gyrus, right corpus callosum, right thalamus, right supramarginal gyrus* and *the right middle and superior temporal gyrus.* The control group showed significant activation in the *right anterior and posterior cerebellum, right middle and superior temporal gyrus, right middle frontal gyrus, right insular cortex, right supramarginal gyrus* and *the right precentral gyrus.* The common functional areas activated during the active condition for the both the intervention and controls groups were *the right anterior and posterior cerebellum, right supramarginal gyrus, right insular cortex, right middle and superior temporal gyrus and the right middle frontal gyrus* (chapter four). Activation of a number of similar areas was expected as both study groups were patients with FMS, although it was not expected that the activations would be identical due to within-group and between-group variations.

Similar to the results reported for the pilot study (phase one), the *right insular cortex* was found to be significantly activated (p<0.0000) for both the intervention and control groups during the active>passive condition at baseline. To reiterate, the insular cortex is believed to be involved in consciousness, emotions, perception, motor control, self-awareness, cognitive functioning, and interpersonal experiences, processing of negative emotions i.e. disgust, anxiety and risky/moral decision making; related to the awareness of threat; empathic pain perception; processing of fearful or disgusted faces; in the anticipation of electric shocks and has been associated with pain catastrophization (Jabbi et al., 2008; Gracely et al., 2004). Again, these previously reported functions for the insular cortex, may explain the activation of the insular cortex when subjects were exposed to the active visuals depicting exercise activities during the active>passive condition in this study. Subjects may have related a particular fearful feeling or in fact catastrophized toward a particular exercise activity, although this cannot be stated for certain. Further research is however warranted to

investigate the exact involvement of the insular cortex in the processing of fearful emotions and catastrophization toward visuals of exercise activities in patients with FMS.

Right anterior and posterior cerebellum activation was significant (p<0.000) (chapter four) for both the intervention group and the control group during the active>passive condition. To reiterate, the cerebellum plays an important role in motor control, but may also be involved in some cognitive functions such as attention and language, and affective regulation such as regulating of fear and pleasure responses (Baillieux et al., 2008, Stoodley et al., 2010). The functions currently reported for the cerebellum can possibly explain the significant activation of the anterior and posterior cerebellum for the intervention group and control group in this phase of the study when the subjects were exposed to visuals of exercise activities during the active condition. Although we cannot be certain if the activation of the anterior and posterior cerebellum were exclusively associated with pain catastrophization towards the exercise activities depicted in the active visuals, again we cannot for certain discard this finding. Regardless, unlike the findings reported for the pilot study, the activation of both the anterior and posterior cerebellum in this phase of the study concurs further with the findings of Gracely *et al.* (2004) who reported that the anterior and posterior cerebellum may be associated with pain catastrophization in patients with FMS. Further research is however warranted to confirm the involvement of the anterior and posterior cerebellum in the processing of pain catastrophization and fear towards visuals of exercise activities in patients with FMS.

Significant activation (p<0.000) (chapter 4) in the *right middle frontal gyrus* was commonly found in both the intervention group and the control group during the active>passive condition. The same result was found in the FMS subject group in phase two of this study. To reiterate, the middle frontal gyrus is involved in high-level executive functions and decision-related processes such as cognitive control, working memory, semantic processing, target detection, memory retrieval, recognition, prospective memory and processing of

emotional stimuli (Talati et al., 2005). In addition, it has also been reported that the middle frontal gyrus may be associated with pain catastrophization in high catastrophizing patients with FMS (Gracely et al., 2004). These functions reported for the middle frontal gyrus may explain activation of this area for both study groups during the active>passive condition since both groups were FMS subjects. Both the intervention and control groups would most probably have seen the active visuals (visuals depicting exercise activities), recognized what the visual was depicting (recognition), retrieved a memory related to that particular activity depicted in the visual (memory retrieval), and then either processed an emotion towards that particular activity depicted in the visual (processing of emotional stimuli) or may have thought of what they would feel if they did the activity (prospective memory), and may even have catastrophized toward the exercise activities (as mentioned in phase two). Although this reaction to the active visuals cannot be stated for certain, again, it does provide a logical explanation for the activation of the middle frontal gyrus in both the intervention and controls groups during the active>passive condition in this phase of the study. Further research is however warranted to investigate the role of the middle frontal gyrus in processing emotions and constructs such as pain catastrophization toward exercise activities in patients with FMS.

The *right superior temporal gyrus* situated in the temporal lobe of the human brain, is believed to play an important role in integrating previous actions and successful outcomes into one's decision-making strategy and contains the primary auditory cortex, which is responsible for processing sounds and comprehension of language (Steinschneider et al., 2011). Since the task presented to the subjects during the fMRI scan did not include verbal input, significant activation $p<0.000$) of the superior temporal gyrus for the intervention group and control group during the active>passive condition can most probably be attributed to the subjects thinking of themselves doing the activity depicted in the visuals and then deciding if they would do the activity again. Although this is pure speculation, and further research is warranted, the fact that significant activation of the superior temporal gyrus was found for the

intervention and control group during the active>passive condition may perhaps indicate that the subjects may have made a decision based on previous experiences while doing the exercise activity depicted in the visual. We may however not know what the decision was based on these results, but we can speculate that the activation of the superior temporal gyrus for both groups during the active>passive condition indicates that some sort of decision was being made during exposure to the visuals of exercise activities.

The *right middle temporal gyrus* is involved in a number of cognitive processes, including semantic memory processing, language processes, and integrating information from different senses (Onitsuka et al., 2004). Significant activation ($p<0.000$) (chapter 4, table ?) of the middle temporal gyrus was found for both the intervention and control group during the active>passive condition at baseline. Based on the previously reported functions of the middle temporal gyrus (Onitsuka et al., 2004), activation of this area during the active>passive condition for both study groups can most probably be explained. Simply stated, the subjects may have looked at the visuals depicting the exercise activities, identified what each visual was depicting and may have processed a memory linked to that particular exercise activity. Again, this is speculation and further research is warranted to ascertain why the middle temporal gyrus would activate only when looking at visuals of exercise activities and not visuals of passive activities in patients with FMS.

The *right supramarginal gyrus* was significantly activated for both the intervention and control group during the active>passive condition at baseline. Since the supramarginal gyrus is believed to contribute to the phonological aspects of word processing and play a role in visual word recognition (Sliwinska et al., 2012); activation of this area during the active condition in this study was puzzling. Reasons for this confusion are based on the fact that no visual words were presented to the subjects at any time during the scanning process. The written instructions to prepare the subjects for the fMRI scans were screened prior to the actual scanning procedure. In addition, the first four scans were discarded, so even if the

scanning procedure accidently began while the subject was still reading the instructions (which we made every attempt to avoid), any brain activations acquired during this time would have been discarded. What is interesting is that both the intervention and controls groups indicated significant activation in this area during the active>passive condition. If however, one considers a previously reported alternative function of the supramarginal gyrus, it may help to explain the activation of this area for both groups during the active>passive condition. According to Russ *et al.* (2003), the supramarginal gyrus, in addition to the middle and superior gyrus, as well as the postcentral gyrus, may be involved in the enactment effect of memory. Enactment effect of memory is basically "learning by doing" or "encoding by performing" whereby performing a task verbally provided improves subsequent memory performance (Engelkamp et al., 1998 & Nilsson et al., 2000 cited in Russ et al., 2003). Despite the involvement of the other mentioned areas, the supramarginal gyrus was however believed to play a central role in this function (Russ et al., 2003). There are however various steps in enactment of memory procedures (Russ et al., 2003), and since the subjects did not enact the activity they were exposed to during the fMRI scan to memorize it, they may have elicited activation of the supramarginal gyrus in preparation of enacting what was being shown. This is however pure speculation and further research is warranted to ascertain the role of the supramarginal gyrus when an individual is exposed to visuals of various activities.

5.4.3.2 Post-intervention between-group comparisons

Post-intervention, the intervention group continued to show significant activation (p<0.000) in the posterior cerebellum only during the active>passive condition. The control group showed significant activation (p<0.000) in the anterior cerebellum, superior parietal lobe, inferior frontal gyrus and the middle frontal gyrus during the active>passive condition.

Right posterior cerebellum activation was still significant (p<0.000) (chapter 4) for the intervention group during the active>passive condition post-intervention. As mentioned at

baseline for this group, the cerebellum plays an important role in motor control, but may also be involved in some cognitive functions such as attention and language, and affective regulation such as regulating of fear and pleasure responses (Baillieux et al., 2008, Stoodley et al., 2010) and may be associated with pain catastrophization (Gracely et al., 2004). . What is however interesting is that the posterior cerebellum was the only functional area that remained significantly activated post-intervention for the intervention group. And furthermore, if compared to the activation of the posterior cerebellum at baseline for this group, it seems activation in this area decreased. Although this finding may imply that the VRET program was effective in reducing activation in areas associated with pain catastrophization, because we cannot be sure if activation of the posterior cerebellum during the active>passive condition for this group was entirely associated with pain catastrophization, we cannot make a conclusive statement about the efficacy of the VRET program on pain catastrophization in patients with FMS in this study. Further research is therefore warranted to confirm the involvement of the posterior cerebellum in the processing of pain catastrophization and fear towards visuals of exercise activities in patients with FMS.

Anterior cerebellum activation was still found to be significant ($p<0.000$) (chapter 4) for the control group during the active>passive condition post-intervention. The posterior cerebellum was no longer found to be significantly activated in the control group post-intervention during the active>passive condition. Although we cannot state for certain why the anterior and not the posterior cerebellum remained activated for the control group post-intervention, it seems that like the intervention group, the control group showed less activation in the anterior cerebellum than found for this group at baseline. Further research is however warranted to confirm the involvement of the anterior cerebellum in the processing of pain catastrophization and fear towards visuals of exercise activities in patients with FMS.

Interestingly however, significant activation ($p<0.000$) of the *superior parietal lobe, middle frontal lobe* and *inferior frontal gyrus* were found for the control group post-intervention

during the active>passive condition, despite the fact that these areas were not found to be significantly activated at baseline for this group. Though we cannot say for certain why significant activation of different functional areas were found post-intervention compared to baseline for this group, we assume that the variation in activations from baseline to post-intervention may have been due to a number of logical explanations. Firstly, the most obvious reason for this finding could have been due to the small sample size included in this phase of the study. In addition, two subjects were lost to follow-up and post-intervention data was not acquired for these patients, which further reduced the sample size. It is expected that in such a small sample size, even one loss to follow-up would be detrimental to the overall group results, and may have confounded the findings considerably, However, since we cannot be sure that the small sample size was the reason for this strange finding, we have to view these findings with caution. Another possible reason for the unexpected findings could have been due to the fact that two of the control subjects were extremely anxious to return to the scanner, post-intervention. When asked why they were so anxious since they had already undergone the procedure, the one subject could not give an answer and the other claimed that she was scared after watching a documentary of how someone died following an fMRI scan. After failing to find the documentary the subject was referring to, the principal researcher resorted to negotiating with the subjects and highlighting the fact that they had already undergone the procedure and nothing had happened to them. Unfortunately, convincing the subjects took a longer than expected, and eventually when they agreed to undergo another fMRI scan, a few weeks had already passed. Essentially, the subjects underwent their post-intervention scans only seven and eight weeks following the start of the intervention, respectively, instead of only three to four weeks. This finding may also be due to the fact that a longer time period passed between the baseline scans and the post-intervention scans for the control group than the intervention group. Considering the fact that the inferior frontal gyrus is believed to play a role in catastrophization (Gracely et al., 2004) as well as in belief-bias reasoning tasks and deductive reasoning tasks (Tsujii et al., 2010; Tsujii et al., 2011) as previously mentioned;

the activation of the inferior frontal gyrus post-intervention for subjects that may have had certain beliefs (fear) about the scanner, is therefore logical. Further research is however required to ascertain the exact involvement of the right inferior frontal gyrus in pain catastrophization and belief-bias reasoning in patients with FMS. In addition, larger studies are recommended for studies like this since loss to follow-up would not be as severe and not affect study outcomes as much.

In conclusion, although it was found that the intervention group showed a reduced number of functional areas activated following a three-week VRET exercise program, when compared to the control group, the results of this phase of the study should be viewed with caution. Simply stated, the novel concept of a VRET program as a treatment for pain catastrophization in patients with FMS set out to be tested in this research, could neither be proven nor negated with the findings of this phase of the study. Various drawbacks which were present may have inadvertently affected the outcome of this phase of the study and should be addressed in future research. Since additional areas were found to be significantly activated post-intervention for the control group, we cannot say for certain that the reduced activation for the intervention group in the functional areas associated with pain catastrophization post-intervention was due to the efficacy of the VRET program, as the control group also showed reduced activation in functional areas associated with pain catastrophization. However, failure to provide conclusive preliminary evidence for the VRET program as a treatment for pain catastrophization in patients with FMS used in this study does not necessarily mean that none exists. It may just mean that we cannot prove it with the group we tested or the methods we used in this research. The findings of this phase may not be conclusive due to the limitations experienced for the control group post-intervention. However the findings do provide sufficient interesting information for the further development and testing of a VRET exercise program as a treatment for pain catastrophization in patients with FMS. Further research is however warranted to test the effect of this program on pain catastrophization in patients with FMS.

5.5 Overall limitations to this research

Proof-of-concept research studies are inherently limited by various obstacles which are either anticipated at the start of the study, or are unexpectedly encountered during the study. However, due to the nature or purposes of most proof-of-concept studies, all obstacles may not necessary be viewed as a negative aspect, but rather as an enlightening one. Conducting smaller proof-of-concept studies are essential in research since they provide the foundation for further investigation of an intervention without the excessive financial overheads which often accompany a larger study. Smaller, proof-of-concept studies like the one presented in this thesis are a good preliminary exercise for presenting new and innovative interventions or techniques (Kinugasa et al., 2004) and provides a good foundation for testing the logistics and methodology of a study before embarking on a larger, more expensive study. Every aspect of the methodology for each individual study included in this research could be scrutinized following execution of the studies. Improvements on these methodological aspects can therefore now be recommended to ensure that future studies incorporate a more robust methodology to attain more accurate results. Proof-of-concept studies therefore provide researchers with the opportunity to investigate the feasibility of further development and testing of a novel intervention.

The most obvious limitation to this study was the small number of subjects included at the various stages of this study, especially the main exploratory studies (chapter four). Besides limiting the ability to generalize the results of this study to other populations, the probability of errors occurring could not be minimized sufficiently due to the small sample size used in this study (Osborne et al., 2004). The small sample included may have inadvertently affected the outcomes of this study, and essentially interpretation of the results and subsequent conclusions should be viewed with caution. The initial concept we set out to prove however was fundamentally unique and justified, but requires further investigation to confirm the findings of this study. It is recommended that a randomized controlled trial including a larger

sample be conducted based on a similar concept and methodology presented in this research.

Furthermore, it is more difficult to detect even subtle differences in outcomes between groups in smaller study samples. According to Cousineau *et al*. (2010), the influence of outliers and its effect on the outcome of a study is greater when the study sample is small. In small study samples, even a few outliers would distort the group results, and this distortion can either be in a negative or positive direction (Cousineau et al., 2010). In the current study this would explain the reasons for certain areas found to be significantly activated when single-subject analyses were done, but when group analyses were done, the areas were no longer found to be significant (chapter four). In addition, two subjects of the 12 initially included in this last phase of the final study were lost to follow-up for various reasons. The one subject's husband passed away during the study period, and the other moved from her previous address and left no forwarding address. All attempts were made to locate these patients/or convince them to return to the study and re-scan them post-intervention. In the end, however, post-intervention analyses of the data were done on the post-intervention data acquired for ten of the subjects and only the baseline data were used for the subjects lost to follow-up, which may have affected the results of this study. Since the study sample was small to begin with, the additional subjects lost to follow-up had a greater impact on the results attained in this study. Larger sample sizes incorporated into future studies may therefore provide better insight into the usefulness and effect of a VRET program as a treatment for pain catastrophization in patients with FMS.

Although every effort was made to ensure that the visuals included in the final fMRI task were the most appropriate to elicit the construct of interest *viz.* pain catastrophization, the development of an fMRI task may require much more than was possible in this study. Some fMRI tasks take several years to develop and involve the testing of thousands of subjects, before the task is passed for further use. In this study, two pilot studies and a focus group

session were conducted to assist us in developing the most optimal fMRI task for this study. Time and financial constraints however prohibited us from extending the validation of the fMRI task indefinitely. Subjects may have become bored or may have ceased to pay attention to the task for the entire duration of the scan which could have influenced the activations in the brain and lead to incorrect results attained. Subjects may also have become familiar with the visuals presented in the fMRI tasks and may not have reacted the same way on seeing the same visuals a second time which could have had an effect on the results attained during the post-intervention scans. We would however recommend that the tasks used in this study be further validated in larger samples to ensure that the tasks are indeed optimal. Perhaps it could be recommended that more visuals be included in the task, as only six visuals of each type of activity were included in the task.

Another drawback identified that may have contributed to the inconclusive findings of this study, may be the current design of the VRET intervention used in this study. Since the design of the VRET exercise program used in this study was provisional, and no VRET program currently exist for pain catastrophization in patients with FMS, the efficacy of the intervention may have been affected by the design of the program. Roughly based on previous literature regarding the basics of CBT (Wright., 2006), and the results of the profile study; in retrospect the VRET program used in this study may not have been adequately designed to conclusively prove its efficacy for pain catastrophization in patients with FMS. For this reason, the results of this study should be viewed with caution and the possibility of a VRET exercise program as a treatment for pain catastrophization in patients with FMS should not be entirely discarded. More time and effort is therefore needed to develop and test a more robust VRET program for pain catastrophization in patients with FMS.

Similarly, the duration of the VRET intervention may not have been adequate and may have inadvertently affected the results of this study. The VRET program was designed based on the results of the preliminary studies conducted in this research and on previous literature

(Wright., 2006; Rodero et al., 2008). However, since a VRET program has never been designed or tested before, the information available to develop the preliminary VRET program for use in this study may not have been sufficient. Furthermore, due to the nature of this research, the unforeseen obstacles which arose while conducting this study, and the excessive efforts that may have been placed on other aspects of the research (such as developing the fMRI task); the time spent on developing a better VRET program for this study was limited. Again, due to these reasons, the results of this study should be viewed with caution and the possibility of further developing a VRET program as treatment for pain catastrophization in FMS should not again be entirely discarded. Further research is therefore required to design and validate a proper VRET exercise program for pain catastrophization in patients with FMS.

Furthermore, it is admitted that in retrospect this research was a great opportunity to ascertain a more in-depth profile of the patients with FMS living in and around the Cape Metropole area of the Western Cape, South Africa. Since developing culturally and linguistically appropriate outcome measures were a primary objective in this research to ensure that the results obtained were valid and accurate, establishing the profile of this group of patients was not a primary objective. In addition, it may be questioned why other outcome measures were not measured in this study, outcome measures which would be deemed necessary by others in the field. For instance, one major limitation in this study was the fact that depression levels were not measured in this study. Including a depression scale in any pain catastrophization or FMS study would probably be deemed mandatory (Gracely et al., 2004). Furthermore, depression was not adjusted for in this study, which may also be viewed as a major limitation to this study. In hindsight, the reasons for excluding a measurement of depression in this study were based on the fact that depression is not a common area for physiotherapists to be involved in. The same thing may however be said about physiotherapy and fMRI scanning of the brains. Similarly, quality of life was also not measured in the sample included in this study. Again, the access to the patients in this study

presented the perfect opportunity to measure quality of life outcome measures which would have painted a greater picture of the burden of FMS in a developing country like South Africa. However, again in our defense, we anticipated that the subjects would have to complete a larger battery of outcome measures and would probably not have been as enthusiastic to participate in the study if they were bombarded to a large amount of questionnaires. We therefore decided to limit the amount of outcome measures to a manageable number as the outcome measures had to be cross-culturally adapted and validated in the study population prior to their use later in the research study. At the time of deciding which outcome measures were most appropriate to be included in the research, we based our decision on the main hypothesis and the main objectives of this study. We however recommend that further research be conducted among a larger group of patients with FMS living in South Africa to establish a more detailed profile of these patients as well as ascertain the burden of FMS on the individual, society, economical status, healthcare sector and the government of South Africa.

In addition, the information regarding the onset of FMS in the subjects included in this study was not established. Currently, the aetiology of FMS remains unknown (Peterson et al., 2007). Information pertaining to the onset of FMS, or a specific event preceding the condition (possible trigger), may have provided insight into the mechanisms of FMS or into triggers which may contribute to the development of the disease. It would have been interesting to establish if the stressors placed on South African women every day are unique and if they contribute to the development of the disease, as well as the maintenance of chronic pain and severity of FMS symptoms. It is therefore recommended that future studies include establishing the mechanisms which underpin the development of FMS in the South African population.

It has to be mentioned that another pitfall to this study may have been the period of time which lapsed between the acquisition of the baseline scan and post-intervention scan.

Following the intervention, subjects had to return to CUBIC to undergo a post-intervention scan. However, due to circumstances, all subjects (in the intervention and control groups) did not undergo a post-intervention scan exactly three weeks following the start of the intervention as planned. Reasons for this delay in re-scanning of patients was mainly due to the fact that there was a delay in booking appointments for the re-scans within the expected time frame at CUBIC, and then in ensuring that these appointments were convenient for the subjects to attend. Some subjects therefore only underwent their post-intervention scan six or eight weeks following the commencement of the intervention. This delay in re-scanning the subjects post-intervention and the variation in time periods between baseline and post-intervention scans for subjects may have affected the post-intervention results, inadvertently affecting the overall outcome of this study. Future studies incorporating an fMRI component should ensure that the period between the baseline and the post-intervention scans are similar for each patient and for each study group and are conducted within a reasonable time-frame.

5.6 Implications of the findings of this research

5.6.1 Implications for patients with FMS in South Africa

Though the findings of the research presented in this thesis do not provide conclusive evidence for the efficacy of a VRET exercise program for pain catastrophization in patients with FMS; the concept of introducing such a program into the management of FMS is not entirely ridiculous. Fundamentally, by reducing pain catastrophization towards exercise activities in patients with FMS, fear-avoidance behaviours should be reduced and compliance towards prescribed exercise programs should be increased. The real benefits of exercise in FMS would therefore be realized by more patients and health providers. Despite the recognition that the management of pain catastrophization warrants urgent attention in the overall management of FMS, a dearth of research still remains into finding effective management strategies for the treatment of pain catastrophization in patients with FMS. The

current research therefore provides the possibility of further developing a specially-designed VRET exercise program which seems to show promise in reducing pain catastrophization in patients with FMS.

5.6.2 Implications for the Physiotherapy practice

The concept of a novel VRET exercise program as a treatment for pain catastrophizing in patients with FMS that was tested in this research, and the rather promising suggestion that this program may be worth further investigation; provides physiotherapists, with the possibility that we are on the brink of developing a tool to address issues such as poor patient compliance in clinical practice, which often hinders the successful management of FMS. By incorporating a VRET exercise program into physiotherapy practices, the premise is that physiotherapists will not only be involved in prescribing exercise therapy in the management of FMS, but will also become more involved in changing existing negative thoughts (catastrophizing thoughts) that the patient may have about exercises, possibly increasing compliance towards exercise programs among FMS sufferers.

5.6.3 Implications for the public sector of South Africa

At this stage, the feasibility of implementing a VRET exercise program as a treatment for pain catastrophization in the public sector of South Africa cannot conclusively be determined. Although the results of the research presented in this thesis does provide preliminary support for further development and testing of a VRET exercise program as a treatment of pain catastrophization in patients with FMS. Until a proper VRET exercise program is developed and tested, the implications for the public sector cannot be provided. Further research is therefore recommended not only to provide evidence for the use of a VRET exercise program in the public sector of South Africa, but also to establish if it would be feasible to incorporate such a program into the current management of FMS in the public sector. Various aspects of the intervention would have to be considered including the time it would take the clinician to administer the intervention, the number of times the patient would

have to attend sessions, the cost of transport, etc. Although the intervention in this study was tested in patients with FMS registered as a public hospital in South Africa, the intervention itself was not tested within a public health setting. For this reason, extrapolation of the results of this research cannot yet be made conclusively, towards the public health sectors.

CHAPTER SIX

CONCLUSION

The results of the research presented in this thesis highlight the many research questions which need to be addressed before a complete understanding of the benefits of the incorporation of a novel VRET exercise program for the treatment of pain catastrophization among patients with FMS is developed. This research identified a number of areas for further investigation regarding patients with FMS and the uptake and maintenance of treatment programs. Although it may be many years before an adequate management strategy for treating pain catastrophization in FMS is successfully implemented in clinical practices across the globe to improve patient compliance; the findings of this research significantly add to the current body of knowledge regarding the possibility of targeting cognitive behavioural strategies like pain catastrophization often observed in chronic pain patients within the physiotherapy practice scope. This research further emphasizes the importance of acknowledging that FMS management should not be approached according to the traditional medical model, but rather according to a compassionate bio-psychosocial model. Simply prescribing treatments to patients with FMS is not enough. Health professionals need to address the factors which prohibit patients from adhering to prescribed treatments so as to gain maximum benefits. There has thus been a shift from simply trying to find effective treatments to finding effective strategies which aim to improve compliance among patients towards these effective treatments. This research therefore significantly contributes to a new era of research relating to finding effective strategies whereby exercise programs and other treatment modalities for patients with FMS can be successfully implemented and maintained, and not be hampered by external barriers (such as costs) and internal barriers (such as poor compliance).

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APPENDICES

APPENDIX 1: SOCIO-DEMOGRAPHIC FORM (English version only)

SOCIO-DEMOGRAPHIC QUESTIONNAIRE — Form 2

OFFICE USE ONLY
Study number: VR ◯ -- ◯
Date: ____/____/20____

PLEASE START HERE: *Complete each question in each section and mark the appropriate box with an* ***X****, where applicable.* *None* *of this information will be made public, so please be honest.*

Date of birth DD / MM / YYYY **Age:** ____ years

Gender: Female | Male **Nationality:** South African | Other:

Ethnic group: Coloured | Black | White | Asian | Other:

Area/town you live in: _____ **Contact no:** _____

Employment:

Still at school	At University/Tech/College	Unemployed	Social/Disability grant
Pensioner	Medically boarded	Self-employed	Casual worker
Housewife	Permanently employed	Occupation, if working:	

Marital status: Single | Married | Separated | Divorced | Widowed

No. of Children: ____ **No. of children under the age of 18y:** ____

Highest level of education: Standard 5 | Matric | University/Tech/College | Other:

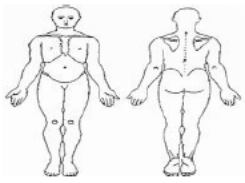
The following section relates to your fibromyalgia symptoms and other conditions and information.

1. How long ago were you first told you had fibromyalgia? ____ **years ago**

2. Which of the following symptoms do you experience? (You may mark more than 1 box)

Pain	Chronic headaches	Muscle pain	Muscles twitches	Joint pain	Stiffness	Nausea
Chest pain	Dizziness	Tenderness	Vision problems	Irritable Bowel	Bladder problems	
Skin conditions	Heavy period pain	Chronic fatigue	Sleep disorders	Weight gain	Anxiety	
Depression	Memory loss	Sensitivity	Mood swings	Other:		

3. Where on your body do you experience pain/symptoms? (You may mark more than 1 box)



All over body	Head	Neck	Shoulders	Arms	
Wrists	Hands	Whole Back	Upper back	Lower back	
Buttocks	Legs	Hips	Knees	Ankles	Feet
Other areas:					

>>>>>> PLEASE TURN THE PAGE OVER >>>>>>

4. How bad is your pain/symptoms at this moment?

Not bad at all	Mild	Average/moderate	Severe	Unbearable

5. When is your pain/symptoms the worst? (You may mark more than 1 box)

All the time	At rest	Morning	Night	During day	Winter	Summer
During or after physical activities/exercises	Other times:					

6. How <u>often</u> do you experience pain/symptoms?

All the time	Everyday	Every 2nd day	2 to 3 times a week	Once a week	Once a month
Hardly ever	Never	Other times:			

7. Which of the following activities <u>increase</u> your pain/symptoms? (You may mark more than 1 box)

Doing nothing / resting	Sitting for long periods	Walking for far distances	Standing for long periods
Driving	Travelling with public transport	Cleaning the house	Doing/hanging the washing
Cooking	Sweeping/mopping/vacuuming	Washing/brushing hair	Dressing/undressing
Working	Bathing/showering	Exercising	Other:

8. Which treatments <u>do or did you</u> receive for your pain/symptoms? (You may mark more than 1 box)

Physiotherapy	Occupational therapy	Psychology/Psychiatry	Acupuncture	Reflexology
Cognitive-behavioural therapy		Exercises	Hydrotherapy/pool therapy	
Medication/tablets (please list names):				
Other treatments:				

9. What <u>other conditions</u> do you suffer from, besides fibromyalgia? (You may mark more than 1 box)

Cancer	High blood	Diabetes	Osteoarthritis	Rheumatoid	Epilepsy	Physical disability
Chronic lung condition		Chronic heart condition		Chronic kidney/liver condition	Lupus	Allergies
HIV/AIDS	Claustrophobia (fear for small spaces)		Other:			

10. Have you ever abused drugs, alcohol or any other substances?	Yes	No
11. Have you ever been in a mental institution for a mental disorder?	Yes	No
12. Do you smoke?	Yes	No
14. Are you currently on medication for depression?	Yes	No
15. Is it possible for you to stop taking your anti-depression medication?	Yes	No

END. Thank you.

APPENDIX 2.A: GPPAQ (English)

GENERAL PRACTICE PHYSICAL ACTIVITY QUESTIONNAIRE * Form 5

OFFICE USE ONLY
Study number: VR ◯ -- ◯
Date: ____/_____/20____

The purpose of this questionnaire is to find out **how active you are in your everyday life**. Please answer all the questions. Please ask the researcher/assistant if you are not sure what is being asked or what to do.

No	**What does your work/job involve?** Choose **ONE** of the following nine options	Mark **one** option with an **(X)**
1	**I am currently not working** (e.g. retired, unemployed, boarded, etc.)	
2	**Sitting behind a desk all day** (e.g. factory worker, office job, etc.)	
3	**Driving most of the day** (e.g. representative, truck driver, delivery job, taxi driver, etc.)	
4	**Standing in more or less one place most of the day** (e.g. hairdresser, teacher, counterhand, machine operator, etc.)	
5	**Walking around most of the day** (e.g. security guard, delivery boy, door-to-door salesperson, etc.)	
6	**Light physical effort with a few types of different activities** (e.g. child minder, cook, librarian, etc.)	
7	**Medium physical effort, using moderate body strength** (e.g. hospital nurse, plumber, cleaner, carpenter, etc.)	
8	**Heavy physical effort, heavy machinery work, physically exhausting** (e.g. construction worker, scaffolder, etc.)	
9	**Physical exercises/activity/sport most of the day** (e.g. gym instructor, coach, body builder, etc.)	

No	**Approximately, how many hours in total did you spend on the following activities in the past week?**	**Number of hours per week**
1	Physical exercises/sport	
2	Walking including shopping, to friends, clinic, etc.	
3	Housework/gardening/childcare	
4	Other types of physical activity (specify):	

On average, how fast or slow would you say you walk? *(mark **one** block with an **X**)*				
Very slow	**Slow**	**Average**	**Fast**	**Very fast**

END. Thank you.

1 *LD Morris Virtual reality and Fibromyalgia (PhD 2010-2012) Div. Physiotherapy, FHS, Stellenbosch University, South Africa*

APPENDIX 2.B: GPPAQ (Afrikaans)

FISIESE-AKTIWITEITSVRAELYS VIR ALGEMENE PRAKTYK* Vorm 5

SLEGS VIR KANTOORGEBRUIK
Studienr.: VR ◯ -- ◯
Datum: ____/_____/20____

Die doel van hierdie vraelys is om uit te vind **hoe aktief u** in u alledaagse lewe is. Beantwoord asseblief al die vrae. Vra die navorser/assistent asseblief as u nie seker is wat gevra word of wat u moet doen nie.

Nommer	Wat doen u by die werk?	Merk een opsie met 'n (X)
1	**Ek werk tans nie** (bv. afgetree, werkloos, dokter het u van werk afgesit, ens.)	
2	**Sit heeldag agter 'n lessenaar.** (bv. fabriekswerker, kantoorwerk, ens.)	
3	**Bestuur vir meeste van die dag** (bv. verteenwoordiger, vragmotorbestuurder, aflewerings, taxibestuurder, ens.)	
4	**Staan op min of meer dieselfde plek vir meeste van die dag** (bv. haarkapper, onderwyser, werk agter 'n toonbank, masjienoperateur, ens.	
5	**Loop meeste van die dag rond** (bv. sekuriteitswag, afleweraar, huis-tot-huis verkoopspersoon, ens.)	
6	**Ligte fisiese inspanning met 'n paar verskillende soorte aktiwiteite** (bv. kinderoppasser, kok, bibliotekaris, ens.)	
7	**Medium fisiese inspanning deur matige gebruik van liggaamskrag** (bv. hospitaalverpleër, loodgieter, skoonmaker, skrynwerker, ens.)	
8	**Hewige fisiese inspanning, werk met swaar masjinerie, fisies uitputtend** (bv. konstruksiewerker, steierbouer, ens.)	
9	**Fisiese oefeninge/aktiwiteit/sport vir meeste van die dag** (bv. gim-instrukteur, afrigter, spierbouer, ens.)	

Nomme	Ongeveer hoeveel uur het u in totaal in die afgelope week aan die volgende aktiwiteite gespandeer?	Aantal uur per week
1	Fisiese oefening/sport	
2	Loop, insluitend inkopies, na vriende, kliniek, ens.	
3	Huiswerk/tuinmaak/kindersorg	
4	Ander tipes fisiese aktiwiteit (spesifiseer):	

Oor die algemeen, hoe vinnig of stadig sou u sê loop u? *(merk een blokkie met 'n **X**)*				
Baie stadig	**Stadig**	**Algemeen**	**Vinnig**	**Baie vinnig**

EINDE. Dankie.

1 *LD Morris Virtual reality and Fibromyalgia (PhD 2010-2012) Div. Physiotherapy, FHS, Stellenbosch University, South Africa*

APPENDIX 2.C: GPPAQ (Xhosa)

IPHEPHA LEMIBUZO YOMTHAMBO JIKELELE*

IFomu ye- 5

ISETYENZISWA YI-OFISI KUPHELA
Inombolo yophando: VR ◯ -- ◯

Umhla : ____/_____/20____

Injongo yeli phepha lemibuzo kukufumanisa ukuba ukhuthele kangakanani ebomini bakho bemihla ngemihla. Nceda uphendule yonke imibuzo. Nceda ubuze umphandi/umncedisi ukuba akuqinisekanga ngento ebuzwayo okanye into ekufuneka uyenzile.

Inani	Umsebenzi wakho ubandakanya ntoni?	Phawula ukhetho lube lunye ngo- (X)
1	**Andiphangeli ngoku** (umz. Ndidla umhlala-phantsi, andiphangeli, ndihlaliswe ngenxa yengulo njl.njl.)	
2	**Ukuhlala edesikeni imini yonke** (umz. umsebenzi wasefektri, umsebenzi wase-ofisini, njl.njl.)	
3	**Ukuqhuba ixesha elininzi losuku** (umz. ummeli, umqhubi wetraka, umsebenzi wokuhambisa izinto, umqhubi weteksi , njl.njl.)	
4	**Ukuma ubukhulu becala kwindawo enye ixesha elininzi losuku** (umz. Umlungisi/umchebi wenwele, utitshala, umncedisi ekhawuntareni, umsebenzisi womatshini, njl.njl.)	
5	**Ukujikeleza ixesha elininzi losuku** (umz. Unogada, inkwenkwe ehambisa izinto, umthengisi ongena ephuma kwiminyango ngeminyango, njl.njl.)	
6	**Intshukumo ekhaphukhaphu kunye neentlobo ezahlukeneyo zemisebenzi** (umz. Umgcini womntwana, umpheki, umsebenzi kwithala leencwadi, njl.n jl.)	
7	**Intshukumo ephakathi, usebenzisa amandla omzimba aphakathi** (umz. Umongikazi wesibhedlele, umtywini wemibhobho yamanzi/ iplamba, umcoci, umchweli, njl.njl.)	
8	**Ukusebenza nzima, umsebenzi womatshini abanzima, umsebenzi odinayo** (umz. umsebenzi owakhayo, umsebenzi wesikhefele/ iskhafolda, njl.njl.)	
9	**Umthambo womzimba/umsebenzi/ umdlalo ixesha elininzi losuku** (umz. Ofundisa umthambo, umqeqeshi, umphakamisi weentsimbi, njl.njl.)	

Inani	Ubuncinane, zingaphi iiyure zizonke ozichithele kule misebenzi ilandelayo kwiveki ephelileyo?	Inani leeyure
1	Umthambo/ umdlalo	
2	Ukuhamba kuquka ukuya kuthenga, ukuya kwizihlobo, ekliniki,njl.njl.	
3	Umsebenzi wasendlwini/ owegadi/ukugcina umntwana	
4	Ezinye iintlobo zemisebenzi yomthambo (Cacisa):	

Ngokwe-avareji, ungathi uhamba kangakanani ngokukhawuleza / ngokucotha? *(phawula ngo-X ibenye)*				
Ngokucotha kakhulu	**Ngokucothayo**	**Ngokulinganayo**	**Ngokukhawuleza**	**Ngokukhawuleza kakhulu**

ISIPHELO. Enkosi.

1 *LD Morris Virtual reality and fibromyalgia PhD project 2010-2012. Div Physiotherapy, FHS, Stellenbosch University, RSA*

APPENDIX 3: Modified PHODA (English version only)

MODIFIED PHODA: EXERCISE ACTIVITIES **Form 7**

OFFICE USE ONLY
Study number: VR ◯ -- ◯
Date: ____/____/20___

The purpose of the following questionnaire is to find out which exercise activities you feel will increase your pain the most or make your symptoms worse. Please ask the researcher/assistant, if you do not understand the instructions or questions, or if you are not sure what you have to do.

INSTRUCTIONS:

On the back of this page you will find **12 pictures** of different types of exercises. Each picture contains a white block in the bottom right-hand corner (your right!).

Please follow the instructions below:

1. Please turn the page around.
2. Take your time and look at each picture.
3. Imagine yourself doing the exercise shown in the picture.
4. Now mark all the pictures where you honestly feel you **cannot** do the exercise shown because you think it will cause you too much pain or make your symptoms worse. **(Place an X in the white box you will find in the bottom right-hand corner of each picture.)**
5. You may mark as many pictures as you like.
6. Once again, if you do not understand anything, or you do not know what to do, please ask the researcher or one of the assistants to help you.

END. Thank you.

APPENDIX 4: PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT: Virtual reality exposure therapy as treatment for pain catastrophizing in Fibromyalgia patients: Proof-of-concept

REFERENCE NUMBER: N10/05/184

PRINCIPAL INVESTIGATOR: Mrs. LD Morris

ADDRESS: Room 1006, 1st Floor, Teaching Block, Faculty of Health Sciences, Tygerberg Campus, Stellenbosch University

CONTACT NUMBER: 0828652261

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part. This study has been approved by the Health Research Ethics Committee (HREC) at Stellenbosch University and will be conducted according to the ethical guidelines and principals of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

Fibromyalgia is a common and complicated chronic pain condition that affects many individuals all over the world. Although there are still many unanswered questions regarding fibromyalgia and its management, what has been found is that exercise is important for patients with fibromyalgia so that their quality of life can be improved. If patients with fibromyalgia do not participate in any exercises, their condition may actually deteriorate. Despite the fact that health professionals involved in the management of fibromyalgia teach patients the importance of exercises; many patients with fibromyalgia still do not want to do any form of exercises. There are many reasons why patients with fibromyalgia fear doing exercises, but most of the time it is because they negatively exaggerate that the exercise activity will harm their bodies and increase their symptoms. This exaggeration is known as *pain catastrophizing*, which is known to play a major role in the maintenance of chronic pain. Therefore, it is important to target pain catastrophizing in the management of patients with fibromyalgia.

To date, only a few studies exist regarding the treatment of pain catastrophizing in patients with fibromyalgia. More specifically, a recent study found that exposure therapy (a treatment which repeatedly exposes you to the situation which you fear, until you do not fear that particular situation anymore) can help treat pain catastrophizing in patients with fibromyalgia. The study used a type of exposure therapy called ‘imagined exposure therapy”. The problem with this type of exposure therapy is that not everybody has a good imagination, and if you

can't imagine situations, then this treatment does not work. Therefore, to overcome this problem, it is proposed that another type of exposure therapy be used, namely *virtual reality exposure therapy*. Virtual reality exposure therapy is a computer-generated environment/situation, which makes you think that you are in the real situation even though you are not, and you don't have to imagine it in your head. The following research project therefore aims to investigate this new idea as a treatment which could assist in altering the negative perceptions patients with fibromyalgia often have towards exercises and help patients with fibromyalgia improve their adherence to exercises, which are beneficial for them. However, before we can determine if virtual reality exposure therapy will work in treating pain catastrophization in patients with fibromyalgia; we first have to check if visual exposure to various exercise activities cognitively triggers pain catastrophizing. In other words, does visual exposure to exercise activities trigger the areas in the brain which are associated with pain catastrophizing? And to do this, we must first do a few things. Firstly, we must find out if patients with fibromyalgia at the Tygerberg Hospital's Rheumatology clinic understand the questionnaires that we want to use in the study. If the questionnaires are not understood among the group of participants we would like to use, then the measurements and data collected will not be correct. Also, we need to find out a bit more about the profile of patients with fibromyalgia attending the Tygerberg Hospital's Rheumatology clinic. Although, it will be a small group, the profile data will help health professionals understand patients with fibromyalgia from the Tygerberg, Cape Town area a little bit better. Therefore, we will conduct a validation and profile study, and this will be phase 1. Then, we must use a brain scan machine to determine if looking at visuals of exercise activities, activates areas in the brain associated with pain catastrophizing in participating patients with fibromyalgia. This will be phase 2 of the project. The last phase of the project will be to determine if exposing patients with fibromyalgia (who have reported that they catastrophize and fear exercise activities) to visuals of exercise activities, reduces pain catastrophizing in these patients. We will also determine if using visual exposure to exercise activities is feasible for this group of participants in terms of the time it takes to administer the intervention, if there are any negative effects, as well as the opinion/thoughts and the acceptance of the intervention by the participants.

The three phases described above will be conducted over the next three years (2010 to 2012). A total number of up to 100 participants, who suffer from fibromyalgia, will be recruited from the Tygerberg Hospital's Rheumatology clinic and Occupational Therapy department during the last half of the year 2010 for phase 1. Participants recruited will participate in the profile and validation study and will be required to complete forms and questionnaires. In early 2011, a sub-group of approximately 20 participants will be selected from the 100 participants who took part in phase 1, and these 20 participants will be invited to participate in phase 2 and 3. Please note that if you agree to participate in phase 1, you are not obligated to agree to participate in phase 2 and 3.

Why have you been invited to participate?

You have been invited to participate in this project because you have been diagnosed with Fibromyalgia, a chronic pain condition and you are currently attending the Tygerberg Hospital's Rheumatology clinic and/or Occupational therapy department.

What will your responsibilities be?

Your responsibilities will be to firstly understand that this is an ongoing project which consists of three phases. If you are eligible and agree to participate in phase 1, you may be selected to participate in the second and third phases. You are however, not obligated to partake in the second and third phases, even if you agree to participate in the first phase. It is also your responsibility to tell us if you suffer from any conditions which may prohibit you from partaking in this project.

Will you benefit from taking part in this research?

If you suffer from fibromyalgia and currently display any negative and fearful responses towards exercise activities, this small project may help reduce those negative feelings you may have towards exercise. After the study you may feel that you can exercise without any fears of hurting yourself and this may benefit you and improve your overall symptoms and quality of life. Your participation in this project will also help future research, health professionals and especially other fibromyalgia patients.

Are there in risks involved in your taking part in this research?

Although the brain scan machine is a rather non-invasive medical test, patients may sometimes experience some complications, such as feelings of claustrophobia when in the machine and interference with medical implants. Other common complaints are that machines are noisy. Headphones or earplugs will therefore be used to help lessen the noise. Similarly, although virtual reality is a relatively harmless intervention, the most common side-effect of virtual reality is nausea and visual perception problems related to motion and visual changes within the virtual environment. Therefore, before you agree to participate in this project, we will first check if you have conditions which will prohibit you from participating in this study. If you have the following conditions, please let us know as you may not be able to participate in this project: cancer; epilepsy, pacemakers, metal implants, claustrophobia, cochlear implants. You can maybe still take part in the first phase of the study, but you will have to be excluded from the second and third phase. Also if you are pregnant let us know, you will then not be allowed to participate in the second and third phase of the project. If you feel nauseous or sick at anytime during the studies, please let us know and the virtual reality or brain scanning will be stopped immediately.

If you do not agree to take part, what alternatives do you have?

You may receive treatment as usual from any health provider you like for your fibromyalgia. There will be no negative consequences if you do not agree to participate in this project. You may also ask the researchers for more information regarding your condition and what other treatment options are available for you.

Who will have access to your medical records?

The only people that will have access to your medical records are the people directly involved in the study and myself. The information collected from you medical records will be treated as private and will be protected from others who should not see them. When the data is printed in the study thesis and is published, your name or details will not appear in the paper and there will be no indication that it was your information.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

The principal researcher is currently registered with the Health Professionals Council of South Africa as a private physiotherapist, and is also privately insured for malpractice and public liability by the South African Society of Physiotherapy. The insurance policy provides indemnity for all cases arising during professional duties; be it in the private or public sector. The insurance policy also indemnifies the insurer (the researcher in this case) against claims arising during the participation of the public in research projects. Therefore, in the unlikely event of an injury occurring during your participation in this research project, the insurance policy will cover all related costs and expenses incurred by you and the researcher.

Will you be paid to take part in this study and are there any costs involved?

No, you will not be paid to take part in the study, but your transport will be covered for each visit, to and from the study venue. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

You should inform your family practitioner or usual doctor that you are taking part in a research study.

You can contact Linzette Morris on 0828652261 if you have any further queries or encounter any problems.

You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I …….…….. agree to take part in a research study entitled:

Virtual reality exposure therapy as treatment for pain catastrophizing in Fibromyalgia patients: Proof-of-concept

I declare that:

I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered.

I understand that taking part in this study is voluntary and I have not been pressurised to take part.

I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

I agree to participate in following phases of the project (please mark one block with an 'x'):

☐ Phase 1 only

☐ Phase 1, and if selected for phase 2 and 3

Signed at (*place*) .....…….. on (*date*) ……...…….. 2010.

.....…….
.....……..

Signature of participant Signature of witness

Declaration by investigator

I *(name)* ……..…… declare that:

I explained the information in this document to ……..

I encouraged him/her to ask questions and took adequate time to answer them.

I am satisfied that he/she adequately understands all aspects of the research, as discussed above

I did/did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.

Signed at (*place*) .....…….. on (*date*) ……...…….. 2010.

.....…….. .....……..

Signature of investigator Signature of witness

Declaration by interpreter

I *(name)* ……..…… declare that:

I assisted the investigator (name) …….. to explain the information in this document to (name of participant) ……..…….. using the language medium of Afrikaans/Xhosa.

We encouraged him/her to ask questions and took adequate time to answer them.

I conveyed a factually correct version of what was related to me.

I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…..…….. on (*date*) ……...……..2010

.....…..…….. .....…..……..

Signature of investigator Signature of witness

APPENDIX 5.A: South African PCS (SA-PCS) (English)

SA-PCS (English)

OFFICE USE ONLY
Study number: VR ◯ -- ◯
Date: ____/____/20____

The purpose of this questionnaire is to find out what your **thoughts and feelings** are when you are in pain. There are 5 options for each question: ***NOT AT ALL, TO A SLIGHT DEGREE, TO A MODERATE DEGREE, TO A GREAT DEGREE***, and ***ALL THE TIME***. For each question, place an **X** in the block that matches to what **DEGREE YOU FEEL OR THINK** a specific way. Please only choose **ONE** block per question. Please ask the researcher/ assistant if you are not sure what is being asked or what to do.

		Place an **X** in appropriate block for each question				
Number	**Feelings/thoughts you have when you are in pain**	**Not at all**	**To a slight degree**	**To a moderate degree**	**To a great degree**	**All the time**
1	When I'm in pain, I worry all the time about whether the pain will ever end.	0	1	2	3	4
2	When I'm in pain, I feel that I can't go on.	0	1	2	3	4
3	When I'm in pain, it is terrible and I think that it is never going to get better.	0	1	2	3	4
4	When I'm in pain, it is awful and I feel it overwhelms me.	0	1	2	3	4
5	When I'm in pain, I feel that I can't stand it anymore.	0	1	2	3	4
6	When I'm in pain, I become afraid that the pain will get worse.	0	1	2	3	4
7	When I'm in pain, I'm keep thinking of the next time I will have pain.	0	1	2	3	4
8	When I'm in pain, I anxiously want the pain to go away quickly.	0	1	2	3	4
9	When I'm in pain, I can't stop thinking about the pain.	0	1	2	3	4
10	When I'm in pain, I keep thinking about how much it hurts.	0	1	2	3	4
11	When I'm in pain, I keep thinking about how badly I want the pain to stop.	0	1	2	3	4
12	When I'm in pain, I feel that there is nothing I can do to stop the pain or make it better.	0	1	2	3	4
13	When I'm in pain, I wonder whether something serious will happen to me.	0	1	2	3	4

1 *LD Morris Virtual reality and Fibromyalgia (PhD 2010-2012) Div. Physiotherapy, FHS, Stellenbosch University, South Africa*

APPENDIX 5.B: South African PCS (SA-PCS) (Afrikaans)

SA-PCS (Afrikaans)

SLEGS VIR KANTOORGEBRUIK
Studienr.: VR ◯ -- ◯
Datum: ____/____/20____

Die doel van hierdie vraelys is om uit te vind wat u dink en voel wanneer u pyn het. Daar is **5** opsies vir elke vraag: ***GLAD NIE, TOT 'N MINDERE MATE, TOT 'N REDELIKE MATE; TOT 'N GROOT MATE; en GEDURIG.*** Vir elke vraag, plaas 'n **X** in die blokkie wat die beste aandui **tot watter MATE u hierdie gedagtes en gevoelens eervaar** wanneer u pyn het**.** Kies asseblief net **een** blokkie per vraag. Vra asseblief die navorser/assistent as u nie seker is wat gevra word of wat u moet doen nie.

		Plaas **X** in geskikte blokkie vir elke vraag				
Nommer	**Gevoelens of gedagtes wat u ervaar wanneer u pyn het**	**Glad nie**	**Tot 'n mindere mate**	**Tot 'n redelike mate**	**Tot 'n groot mate**	**Gedurig**
1	Wanneer ek pyn het, is ek bekommerd dat die pyn nooit sal ophou nie.	0	1	2	3	4
2	Wanneer ek pyn het, voel ek dat ek nie langer kan aanhou nie.	0	1	2	3	4
3	Wanneer ek pyn het, is dit verskriklik en ek dink dat dit nooit beter sal raak nie.	0	1	2	3	4
4	Wanneer ek pyn het, is dit aaklig en ek voel dit oorweldig my.	0	1	2	3	4
5	Wanneer ek pyn het, voel ek dat ek dit nie meer kan verdra nie.	0	1	2	3	4
6	Wanneer ek pyn het, raak ek bang dat die pyn erger gaan word.	0	1	2	3	4
7	Wanneer ek pyn het, dink ek klaar aan die volgende keer wat ek pyn gaan hê.	0	1	2	3	4
8	Wanneer ek pyn het, is ek angstig dat die pyn moet verdwyn.	0	1	2	3	4
9	Wanneer ek pyn het, kan ek nie ophou om aan die pyn te dink nie.	0	1	2	3	4
10	Wanneer ek pyn het, hou ek aan dink hoe seer dit is.	0	1	2	3	4
11	Wanneer ek pyn het, hou ek aan dink hoe graag ek wil hê dat die pyn moet weggaan.	0	1	2	3	4
12	Wanneer ek pyn het, voel ek dat daar niks is wat ek kan doen om dit weg te neem of beter te maak nie.	0	1	2	3	4
13	Wanneer ek pyn het, raak ek bekommerd dat iets sleg met my gaan gebeur.	0	1	2	3	4

1 *LD Morris Virtual reality and Fibromyalgia (PhD 2010-2012) Div. Physiotherapy, FHS, Stellenbosch University, South Africa*

APPENDIX 5.C: South African PCS (SA-PCS) (Xhosa)

SA-PCS (isiXhosa)

ISETYENZISWA YI-OFISI KUPHELA
Inombolo yophando: VR ◯ -- ◯

Umhla : ____/_____/20____

Injongo yeli phepha lemibuzo kukufumanisa ukuba zithini iingcinga noluvo lwakho xa usiva intlungu. Nceda usebenzise indlela yokubala amanqaku ukuphendula yonke imibuzo. **Amanqaku alingana nokuba kukangaphi uziva ngalo ndlela iyodwa.** Nceda ubuze umphandi/umncedisi ukuba akuqinisekanga ngento ebuzwayo okanye into ekufuneka uyenzile.

		Phawula amanqaku ngo- (X)				
Inani	Uluvo okanye iingcinga onazo	Zange	Maxa wambi	Isiqingatha sexesha	Ixesha elininzi	Lonke ixesha
1	Xa ndisiva intlungu, ndiyakhathazeka ukuba ingaba iyakuze iphele na intlungu.					
2	Xa ndisiva intlungu, ndiziva ndingenakho ukuqhubela phambili nobom konke.					
3	Xa ndisiva intlungu, ndicinga ukuba ayisokuze ibe bhetele.					
4	Xa ndisiva intlungu, iyandongamela.					
5	Xa ndisiva intlungu, andikwazi ukumelana nayo konke.					
6	Xa ndisiva intlungu, ndiyoyika ukuba iza kuqaqamba ngaphezulu.					
7	Xa ndisiva intlungu, ndiba sendicinga ixesha elizayo endiza kuba nentlungu ngalo.					
8	Xa ndisiva intlungu, ndifuna ngamandla ukuba intlungu iphele.					
9	Xa ndisiva intlungu, andikwazi ukungacingi ngayo.					
10	Xa ndisiva intlungu, ndicinga njalo ukuba imbi kangakanani.					
11	Xa ndisiva intlungu, ndicinga njalo ngendlela endifuna iphele ngayo.					
12	Xa ndisiva intlungu, ndiyayazi ukuba akukho nto ndinokuyenza ukuyiphelisa okanye ukuyenza bhetele.					
13	Xa ndisiva intlungu, ndiyakhathazeka ukuba kukho into embi eza kundehlela.					

1 *LD Morris Virtual reality and fibromyalgia PhD project 2010-2012. Div Physiotherapy, FHS, Stellenbosch University, RSA*

APPENDIX 6.A: South African TSK (SA-TSK) (English)

SA-TSK (English)

OFFICE USE ONLY
Study number: VR ◯ -- ◯
Date: ____/_____/20____

The purpose of this questionnaire is to find out what your feelings/thoughts are towards physical activity/exercises. There are **4** options for each question, which represent the extent to which you agree or disagree with each statement: "**strongly disagree"; "disagree", "agree";** and **"strongly agree".** For each question, place an **X** in the block that matches **to which extent you AGREE or DISAGREE with the following statement**. Please only choose **ONE** block per question. Please ask the researcher/assistant if you are not sure what is being asked or what to do.

		Place an X in appropriate block			
Number	**Feelings/thoughts**	**Strongly disagree**	**Disagree**	**Agree**	**Strongly agree**
1	I am afraid that I will injure myself when I exercise.	1	2	3	4
2	I feel that if I try to overcome it, my pain will increase.	1	2	3	4
3	My body is telling me that there is something dangerously wrong.	1	2	3	4
4	My pain would probably be relieved if I were to exercise.	1	2	3	4
5	People do not take my condition seriously.	1	2	3	4
6	My condition has put my body at risk for the rest of my life.	1	2	3	4
7	Pain always means that I have injured myself.	1	2	3	4
8	Just because something increases my pain, does not mean that it is bad.	1	2	3	4
9	I am afraid that I will injure myself by accident.	1	2	3	4
10	The safest thing for me is to not do anything that will increase my pain.	1	2	3	4
11	I have this much pain because there is something dangerously wrong with me.	1	2	3	4
12	Although I am in pain, I will be better off if I exercise.	1	2	3	4
13	Pain tells me that I must stop exercising so that I d not injure myself.	1	2	3	4
14	It is really not safe for someone like me, who has fibromyalgia, to exercise.	1	2	3	4
15	I can't do things that normal people do because of my pain.	1	2	3	4
16	Although I have pain, I don't think that it is dangerous.	1	2	3	4
17	No one should have to exercise if they are in pain.	1	2	3	4

1 *LD Morris Virtual reality and Fibromyalgia (PhD 2010-2012) Div. Physiotherapy, FHS, Stellenbosch University, South Africa*

APPENDIX 6.B: South African TSK (SA-TSK) (Afrikaans)

SA-TSK (Afrikaans)

SLEGS VIR KANTOORGEBRUIK

Studienr.: VR ◯ -- ◯

Datum: ____/_____/20____

Die doel van hierdie vraelys is om uit te vind of u enige vrese vir die beweging van u liggaam of vir fisiese aktiwiteit/oefeninge het. Elke vraag het 4 opsies, en die opsies dui aan **hoe sterk u saamstem of verskil** met 'n spesifieke gevoel of gedagte. Vra asseblief die navorser/assistent as u nie seker is wat gevra word of wat u moet doen nie.

		Plaas 'n **X** in geskikte blokkie			
Nommer	**Gevoelens of gedagtes wat u ervaar**	Verskil sterk	Stem nie saam nie	Stem saam	Stem heeltemaal saam
1	Ek is bang dat ek myself sal beseer wanneer ek oefen.	1	2	3	4
2	Ek sal baie meer pyn hê as ek oefen.	1	2	3	4
3	My liggaam sê vir my dat iets nie reg is nie.	1	2	3	4
4	My pyn sal waarskynlik beter raak as ek oefen.	1	2	3	4
5	Mense neem nie my toestand ernstig op nie.	1	2	3	4
6	My toestand het my liggaam in gevaar gestel vir die res van my lewe.	1	2	3	4
7	Pyn beteken altyd dat ek myself beseer het.	1	2	3	4
8	Net omdat iets my meer pyn gee, beteken nie dat dit sleg is nie.	1	2	3	4
9	Ek is bang dat ek per ongeluk myself sal beseer.	1	2	3	4
10	Die veiligste sal wees om niks te doen wat my pyn erger sal maak nie.	1	2	3	4
11	Ek het so baie pyn omdat daar groot fout met my is.	1	2	3	4
12	Alhoewel ek baie pyn het, sal dit beter vir my wees as ek oefen.	1	2	3	4
13	Pyn laat my weet dat ek moet ophou om te oefen.	1	2	3	4
14	Dit is nie veilig vir iemand soos ek, wat fibromialgie het, om te oefen nie.	1	2	3	4
15	As gevolg van my pyn, kan ek nie dinge doen wat normale mense doen nie.	1	2	3	4
16	Alhoewel ek pyn het, dink ek nie dat dit gevaarlik is nie.	1	2	3	4
17	Mense in pyn moet nie geforseer word om te oefen nie.	1	2	3	4

1 *LD Morris Virtual reality and Fibromyalgia (PhD 2010-2012) Div. Physiotherapy, FHS, Stellenbosch University, South Africa*

APPENDIX 6.C: South African TSK (SA-TSK) (Xhosa)

SA-TSK (isiXhosa)

ISETYENZISWA YI-OFISI KUPHELA
Inombolo yophando: VR ( ) -- ( )

Umhla : ____/_____/20____

Injongo yeli phepha lemibuzo kukufumanisa ukuba ingaba unalo na uloyiko ekushukumiseni umzimba wakho okanye ekwenzeni imithambo/ imisebenzi . Nceda usebenzisa indlela yokubala amanqaku ukuphendula yonke imibuzo. Amanqaku alingana nokuba uziva ngamandla kangakanani ngalo ndlela iyodwa. Nceda ubuze umphandi /umncedisi ukuba akuqinisekanga ngento ebuzwayo okanye ukuba kufuneka wenze ntoni.

		Phawula ngo- (X)			
Inani	Uvakalelo okanye iingcinga onazo xa usiva iintlungu	Andingqinelan i kwaphela	Andingqinelan i kancinane	Ndingqinelana kancinane	Ndingqinelana kakhulu
1	Ndiyoyika ukuba ndiza kuzenzakalisa xa ndisenza umthambo.				
2	Ukuba ndenza umthambo, intlungu zam ziza kwanda kakhulu.				
3	Umzimba wam uyandixelela ukuba kukho into engalunganga.				
4	Intlungu yam mhlawumbi iya kuba nesiqabu xa ndinokwenza umthambo.				
5	Abantu abayithathi ngokuxhalabisekileyo imeko yam.				
6	Imeko yam ibeke umzimba wam kwingozi ubom bam bonke.				
7	Ngalo lonke ixesha intlungu ithetha ukuba ndizenzakalisile.				
8	Kuba kukho into eyandisa intlungu yam, loo nto ayithethi ukuba imbi.				
9	Ndinexhala lokuba ndiza kuzenzakalisa ngengozi.				
10	Eyona nto ikhuselekileyo kum kukuba ndingenzi nantonina eya kwandisa intlungu yam.				
11	Ndinale ntlungu ingaka kuba kukho into eyingozi engalunganga kum.				
12	Nangona ndinentlungu, ndiya kuba bhetele xa ndinokwenza umthambo.				
13	Intlungu indixelela ukuba mandiyeke ukwenza umthambo.				
14	Akukhuselekanga kumntu ofana nam, onefibromyalgia , ukuba enze umthambo.				
15	Andikwazi ukwenza izinto ezenziwa ngabantu abaphilileyo ngenxa yentlungu yam.				
16	Nangona ndinentlungu, andiqondi ukuba iyingozi				
17	Akukho mntu ufanele ukwenza umthambo ukuba unentlungu.				

1 *LD Morris Virtual reality and fibromyalgia PhD project 2010-2012. Div Physiotherapy, FHS, Stellenbosch University, RSA*

APPENDIX 7.A: South African FIQR (SA-FIQR) (English)

SA-FIQR (English)

OFFICE USE ONLY
Study number: VR ◯ -- ◯
Date: ____/_____/20____

The purpose of this questionnaire is to find out how **fibromyalgia impacts on your life.** Please answer all the questions. There are 3 subsections to this questionnaire. The instructions for each subsection are given accordingly. Please ask the researcher/assistant if you are not sure what is being asked or what to do.

SUBSECTION 1: How difficult would you say it is for you to do the followings daily tasks? Each question has **5** options. Please only choose **ONE** block per question.

Number	DAILY TASK	Place an **X** in the appropriate block: No difficulty at all	Little difficult	Difficult	Quite difficult	Extremely difficult
1	Brush/comb/wash your hair					
2	Walk for more than 20 minutes					
3	Cook/bake for family					
4	Sweep/wash floors or vacuum carpets					
5	Lift/carry a light/medium weight object like grocery bags					
6	Climb one flight of stairs					
7	Change bed linen/curtains or do/hang up washing					
8	Sit/stand for more than 45 minutes					
9	Go shopping/run errands i.e. go to post office/bank/clinic					

>>>> Please turn over page >>>>

SUBSECTION 2: Please answer the following two questions, which relate to the impact fibromyalgia has had on your life by marking an **X** in the appropriate block. Each question has five options to choose from. Please only choose **ONE** block per question.

	Mark **ONE** block with an (X)			
Question 1 Does fibromyalgia ever stop you from doing something you really want to do?	**Never**	**Sometimes**	**Most times**	**Always**
Question 2 Are you ever overwhelmed by your fibromyalgia symptoms?	**Never**	**Sometimes**	**Most times**	**Always**

SUBSECTION 3: Please rate the severity/level of your symptoms by marking the appropriate box for each question with an **X.** Each question has **5** options to choose from. Please only choose **ONE** block per question.

Number	Symptom	Mark **ONE** block with an (**X**) that best describes the severity of each symptom that you experience				
1	**Pain**	No pain	Mild	Moderate	Severe	Unbearable
2	**Energy**	Lots of energy	Sufficient	Moderate	Low	No energy
3	**Stiffness**	No stiffness	Mild	Moderate	Severe	Extreme
4	**Sleep quality**	Very good	Good	Moderate	Very bad	Extremely bad
5	**Depression**	No depression	Mild	Moderate	High	Extreme
6	**Memory**	Very good	Good	Moderate	Very bad	Extremely bad
7	**Anxiety**	No anxiety	Low	Moderate	High	Extreme
8	**Tenderness:** touch	No tenderness	Mild	Moderate	Severe	Unbearable
9	**Balance**	Very good	Good	Moderate	Very bad	Extremely bad
10	**Sensitivity** to bright light/ noise/smells/temp, etc.	No sensitivity	Mild	Moderate	Severe	Unbearable

APPENDIX 7.B: South African FIQR (SA-FIQR) (Afrikaans)

SA-FIQR (Afrikaans)

SLEGS VIR KANTOORGEBRUIK

Studienr.: VR ◯ -- ◯

Datum: ____/_____/20____

Die doel van hierdie vraelys is om uit te vind hoe **fibromialgie u lewe beïnvloed**. Beantwoord asseblief al die vrae. Daar is 3 onderafdelings vir hierdie vraelys. Vra asseblief die navorser/assistent as u nie seker is wat gevra word of wat u moet doen nie.

ONDERAFDELING 1: Hoe moelik sal jy se is dit vir jou om die volgende te doen? Elke vraag het **5** opsies. Kies asseblief **een** blokkie per vraag.

		Plaas 'n **X** in die toepaslike blokkie				
Nommer	Daaglikse taak	Glad nie moeilik nie	Effens moeilik	Moeilik	Redelik moeilik	Uiters moeilik, kan nie taak doen nie
1	Borsel/kam/was u hare					
2	Om vir langer as 20 minute te loop					
3	Kook/bak vir die gesin					
4	Vee/was vloere of suig matte					
5	Lig en dra 'n voorwerp van ligte/medium gewig, soos inkopiesakke					
6	Klim een stel trappe					
7	Ruil beddegoed/gordyne of doen die wasgoed/hang dit op					
8	Sit/staan vir meer as 45 minute					
9	Doen inkopies/takies bv. om poskantoor/bank/kliniek toe te gaan					

>>>>Blaai asseblief om>>>>

1 *LD Morris Virtual reality and Fibromyalgia (PhD 2010-2012) Div. Physiotherapy, FHS, Stellenbosch University, South Africa*

ONDERAFDELING 2: Die volgende vrae gaan oor die algehele invloed wat fibromialgie op u lewe het. Kies asseblief **een** blokkie per vraag.	Plaas 'n **X** in die toepaslike blokkie			
Vraag 1 Het fibromialgie al ooit gekeer dat u iets doen wat u regtig graag wou doen?	**Nooit**	**Soms**	**Die meeste keer**	**Altyd**
Vraag 2 Word u ooit deur u fibromialgie-simptome oorweldig?	**Nooit**	**Soms**	**Die meeste keer**	**Altyd**

ONDERAFDELING 3: Die volgende vrae gaan oor die erns van u fibromialgie-simptome. Toon asseblief die erns/vlak van u simptome deur die toepaslike blokkie vir elke vraag met 'n **X** te merk. Kies asseblief **een** blokkie per vraag.

Nommer	Fibromialgie-simptoom	Erns/Vlak Merk toepaslike blokkie met 'n X				
1	Pyn	Geen pyn	Lig	Matig	Ernstig	Ondraaglik
2	Energie	Baie energie	Genoeg	Matig	Laag	Geen energie
3	Styfheid	Geen styfheid	Lig	Matig	Ernstig	Uiters
4	Slaapkwaliteit	Baie goed	Goed	Matig	Baie sleg	Uiters sleg
5	Depressie	Geen depressie	Lig	Matig	Hoog	Uiters
6	Geheue	Baie goed	Goed	Matig	Baie sleg	Uiters sleg
7	Angs	Geen angs	Laag	Matig	Hoog	Uiters
8	Teerheid: aanraking	Geen teerheid	Lig	Matig	Ernstig	Ondraaglik
9	Balans	Baie goed	Goed	Matig	Baie sleg	Uiters sleg
10	Sensitiwiteit: helder lig/geraas/reuke/temp.	Geen sensitiwiteit	Lig	Matig	Ernstig	Ondraaglik

APPENDIX 7.C: South African FIQR (SA-FIQR) (Xhosa)

SA-FIQR (isXhosa)

ISETYENZISWA YI-OFISI KUPHELA
Inombolo yophando: VR ◯ -- ◯

Umhla : ____/_____/20____

Injongo yeli phepha lemibuzo kukufumanisa ukuba ifibromyalgia inampembelelo ni kubomi bakho. Nceda uphendule yonke imibuzo. Kukho amacandelwana ama-3 kweli phepha lemibuzo. Emva kokuba ugqibe amacandelwana ama- 2 kweli cala lephepha, nceda utyhile iphepha ugqibezele icandelwana lokugqibela. Nceda ubuze umphandi /umncedisi ukuba akuqinisekanga ngento ebuzwayo okanye into ekufuneka uyenzile.

Yecandelwana lo- 1: Usebenzisa le ndlela yokubala amanqaku ingentla, thekelela ukuba ungathi kunzima kangakanani kuwe ukwenza ezi zinto zilandelayo?

Ina ni.	UMSEBENZI	Akukho bunzima kwaphela	Buncinci ubunzima	Kunzima	Kunzima noko	Kunzima ngokugqithisileyo
		Phawula ibhloko ibenye ngo- (X)				
1	Ukubhrasha/ukukama/ukuhlamba iinwele zakho					
2	Ukuhamba ngaphezulu kwemizuzu engama- 20					
3	Ukuphekela/ukubhakela usapho					
4	Ukutshayela/ ukuhlamba imigangatho okanye ukuvaktyhuma iikhapethi					
5	Ukuphakamisa nokuphatha into ekhaphukhaphu/ephakathi ngobunzima enjengeebhegi zokutya					
6	Ukwenyuka umgangatho omnye wezitezi					
7	Ukutshintsha amashiti ebhedi/iikhethinsi okanye ukuxhoma impahla ehlanjiweyo					
8	Ukuhlala/ukuma ngaphezulu kwemizuzu engama- 45					
9	Ukuya kuthenga/ukwenza izinto ezithile oko kukuthi ukuya eposini/ ebhankini/ ekliniki					

>>>> Nceda utyhile iphepha >>>>

1 *LD Morris Virtual reality and fibromyalgia PhD project 2010-2012. Div Physiotherapy, FHS, Stellenbosch University, RSA*

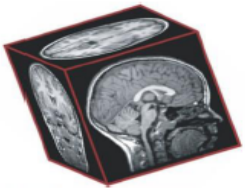
Yecandelwana lo- 2: Le mibuzo ilandelayo imalunga nempembelelo ifibromyalgia enayo kubom bakho jikelele. Nceda wenze uphawu kwibhokisi efanelekileyo ukuphendula umbuzo ngamnye.

Inani	Umbuzo	Phawula ibhloko efanelekileyo ngo (X)			
1	Ingaba ifibromyalgia ikhe ikuthintele ekwenzeni into ofuna ukuyenza ngenene?	Zange	Maxa wambi	Amaxesha amaninzi	Rhoqo
2	Ukhe wonganyelwe ziimpawu zakho zefibromyalgia ?	Zange	Maxa wambi	Amaxesha amaninzi	Rhoqo

Yecandelwana lo- 3: Le mibuzo ilandelayo imalunga nobukhali beempawu onazo zefibromyalgia. Nceda uthekelele ubukhali /umgangatho weempawu zakho ngokuphawula ibhokisi efanelekileyo ibenye ngo- X kumbuzo ngamnye.

Inani	Iimpawu zeFibromyalgia	Ubukhali/ Umgangatho Phawula ibhloko efanelekileyo ngo- (X)				
1	Intlungu	Akukho ntlungu	Zizolile	Ziphakathi	Zibukhali	Azinyamezeleki
2	Amandla	Amandla maninzi	Onele	Aphakathi	Aphantsi/ mancinci	Awekho amandla
3	Ukuqina	Akukho kuqina	Kuzolile	Kuphakathi	Kubukhali	Kugqithisile
4	Uhlobo lokulala	Lulunge kakhulu	Lulungile	Luphakathi	Lubi kakhulu	Lubi ngokugqithisileyo kakhulu
5	Ukudakumba	Akukho ukudakumba	Kuzolile	Kuphakathi	Kuphezulu	Kugqithisile
6	Inkumbulo	Zilunge kakhulu	Zilungile	Ziphakathi	Zimbi kakhulu	Zimbi ngokugqithisileyo kakhulu
7	Ukuxhalaba	Akukho kuxhalaba	Kuphantsi / kuncinci	Kuphakathi	Kuphezulu	Kugqithisile
8	Ukuthamba: kokuphatha:	Akukho kuthamba	Kuzolile	Kuphakathi	Kubukhali	Akunyamezeleki
9	Ukuxhathisa	Kulunge kakhulu	Kulungile	Kuphakathi	Kubi kakhulu	Kubi ngokugqithisileyo
10	Ukuvakalelwa: khazimla ukukhanya/ingxolo/ivumba/ubushushu	Akukho kuvakalelwa	Kuzolile	Kuphakathi	Kubukhali	Akunyamezeleki

APPENDIX 8: Permission granted to conduct study at CUBIC facility



Cape Universities Brain Imaging Centre (CUBIC)

27 May 2010

Linzette Morris
Division of Physiotherapy
Department of Interdisciplinary Health Sciences
Faculty of Health Sciences
University of Stellenbosch
ldmorris@sun.ac.za

Dear Ms Morris

SUPPORT FOR THE IMAGING COMPONENT OF PHD STUDY: VIRTUAL REALITY EXPOSURE THERAPY AS TREATMENT FOR PAIN CATASTROPHIZING IN FIBROMYALGIA PATIENTS

This letter serves to confirm that we are willing to support this study through access to the MRI facility at the Cape Universities Brain Imaging Centre (CUBIC), which is located at the Stellenbosch University Medical School in Cape Town, South Africa. The scans would be performed on a Siemens 3T Magnetom Allegra MRI system.

This core focus of the centre is research and as such the researchers will be assured time on the MRI scanner. Research scans on patients/volunteers will be billed at an hourly rate of R2354 (excl VAT) and will require approval by the Institutional Review Board of the University of Stellenbosch. The CUBIC adheres to strict quality assurance standards and regular calibration scans are done to ensure optimal stability and performance of the MRI equipment. An MRI physicist and two technologists are employed by the centre to assist with all technical aspects of the scan protocols.

We look forward to working with you on this research collaboration. Should you require any further information, please do not hesitate to contact me.

Yours sincerely,

Bruce Spottiswoode, Ph.D., Pr.Eng.

Director, Cape Universities Brain Imaging Centre

Cape Universities Brain Imaging Centre
Fisan Building, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, 7505
Tel: 27-21-938-9646 Fax: 27-21-938-9728 www.sun.ac.za/cubic

APPENDIX 9: Informed consent form (Focus group study)

TITLE OF THE RESEARCH PROJECT: Virtual reality exposure therapy as treatment for pain catastrophizing in Fibromyalgia patients: Proof-of-concept

REFERENCE NUMBER: N10/05/184

PRINCIPAL INVESTIGATOR: Mrs. LD Morris

ADDRESS: Room 1006, 1st Floor, Teaching Block, Faculty of Health Sciences, Tygerberg Campus, Stellenbosch University

CONTACT NUMBER: 0828652261

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part. This study has been approved by the Health Research Ethics Committee (HREC) at Stellenbosch University and will be conducted according to the ethical guidelines and principals of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

Fibromyalgia is a common and complicated chronic pain condition that affects many individuals all over the world. Although there are still many unanswered questions regarding fibromyalgia and its management, what has been found is that exercise is important for patients with fibromyalgia so that their quality of life can be improved. If patients with fibromyalgia do not participate in any exercises, their condition may actually deteriorate. Despite the fact that health professionals involved in the management of fibromyalgia teach patients the importance of exercises; many patients with fibromyalgia still do not want to do any form of exercises. There are many reasons why patients with fibromyalgia fear doing exercises, but most of the time it is because they negatively exaggerate that the exercise activity will harm their bodies and increase their symptoms. This exaggeration is known as *pain catastrophizing*, which is known to play a major role in the maintenance of chronic pain. Therefore, it is important to target pain catastrophizing in the management of patients with fibromyalgia.

To date, only a few studies exist regarding the treatment of pain catastrophizing in patients with fibromyalgia. More specifically, a recent study found that exposure therapy (a treatment which repeatedly exposes you to the situation which you fear, until you do not fear that particular situation anymore) can help treat pain catastrophizing in patients with fibromyalgia. The study used a type of exposure therapy called ‘imagined exposure therapy”. The problem with this type of exposure therapy is that not everybody has a good imagination, and if you

can't imagine situations, then this treatment does not work. Therefore, to overcome this problem, it is proposed that another type of exposure therapy be used, namely *virtual reality exposure therapy*. Virtual reality exposure therapy is a computer-generated environment/situation, which makes you think that you are in the real situation even though you are not, and you don't have to imagine it in your head. The following research project therefore aims to investigate this new idea as a treatment which could assist in altering the negative perceptions patients with fibromyalgia often have towards exercises and help patients with fibromyalgia improve their adherence to exercises, which are beneficial for them. However, before we can determine if virtual reality exposure therapy will work in treating pain catastrophization in patients with fibromyalgia; we first have to check if visual exposure to various exercise activities cognitively triggers pain catastrophizing. In other words, does visual exposure to exercise activities trigger the areas in the brain which are associated with pain catastrophizing? To find the answer to this questions, we must use a brain scan machine to determine if looking at visuals of exercise activities, activates areas in the brain associated with pain catastrophizing in participating patients with fibromyalgia. However, before doing the brain scans, we need to determine whether or not the visuals we use during the brain scans are associated with unnecessary negative emotions or personal negative events. If the visuals are associated with negative emotions or events, then the visuals have to be replaced with other visuals which are not associated with any negative emotions or events. Once we have removed all the visuals which are associated with any negative emotions or events, then we can continue with the main part of the project.

Why have you been invited to participate?

You have been invited to participate in this project because you have been diagnosed with Fibromyalgia, a chronic pain condition and you are currently attending the Tygerberg Hospital's Rheumatology clinic and/or Occupational therapy department.

What will your responsibilities be?

Your responsibilities will be to firstly ensure that you understand the purpose of this project and that the information you provide is the truth.

Will you benefit from taking part in this research?

Your participation in this project will help future research, health professionals and especially other fibromyalgia patients.

Are there in risks involved in your taking part in this research?

For this part of the project there are no risks involved in you participating.

If you do not agree to take part, what alternatives do you have?

You may receive treatment as usual from any health provider you like for your fibromyalgia. There will be no negative consequences if you do not agree to participate in this project. You may also ask the researchers for more information regarding your condition and what other treatment options are available for you.

Who will have access to your medical records?

The only people that will have access to your medical records are the people directly involved in the study and myself. The information collected from you medical records will be treated as private and will be protected from others who should not see them. When the data is printed in the study thesis and is published, your name or details will not appear in the paper and there will be no indication that it was your information.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

The principal researcher is currently registered with the Health Professionals Council of South Africa as a private physiotherapist, and is also privately insured for malpractice and public liability by the South African Society of Physiotherapy. The insurance policy provides indemnity for all cases arising during professional duties; be it in the private or public sector. The insurance policy also indemnifies the insurer (the researcher in this case) against claims arising during the participation of the public in research projects. Therefore, in the unlikely event of an injury occurring during your participation in this research project, the insurance policy will cover all related costs and expenses incurred by you and the researcher.

Will you be paid to take part in this study and are there any costs involved?

No, you will not be paid to take part in the study, but your transport will be covered for each visit, to and from the study venue. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

You should inform your family practitioner or usual doctor that you are taking part in a research study.

You can contact Linzette Morris on 0828652261 if you have any further queries or encounter any problems.

You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled:

Virtual reality exposure therapy as treatment for pain catastrophizing in Fibromyalgia patients: Proof-of-concept

I declare that:

I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered.

I understand that taking part in this study is voluntary and I have not been pressurised to take part.

I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2010.

.....…..…….. .....…..……..

Signature of investigator Signature of witness

Declaration by investigator

I *(name)* ……..…… declare that:

I explained the information in this document to ……..

I encouraged him/her to ask questions and took adequate time to answer them.

I am satisfied that he/she adequately understands all aspects of the research, as discussed above

I did/did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2010.

.....…..…….. .....…..……..

Signature of investigator Signature of witness

Declaration by interpreter

I *(name)* ……..…… declare that:

I assisted the investigator (name) …….. to explain the information in this document to (name of participant) ……..…….. using the language medium of Afrikaans/Xhosa.

We encouraged him/her to ask questions and took adequate time to answer them.

I conveyed a factually correct version of what was related to me.

I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…..…….. on (*date*) ……...……..2010

.....…..…….. .....…..……..

Signature of investigator Signature of witness

APPENDIX 10: Informed consent form (Controls)

TITLE OF THE RESEARCH PROJECT: Virtual reality exposure therapy as treatment for pain catastrophizing in Fibromyalgia patients: Proof-of-concept

REFERENCE NUMBER: N10/05/184

PRINCIPAL INVESTIGATOR: Mrs. LD Morris

ADDRESS: Room 1006, 1st Floor, Teaching Block, Faculty of Health Sciences, Tygerberg Campus, Stellenbosch University

CONTACT NUMBER: 0828652261

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part. This study has been approved by the Health Research Ethics Committee (HREC) at Stellenbosch University and will be conducted according to the ethical guidelines and principals of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

Fibromyalgia is a common and complicated chronic pain condition that affects many individuals all over the world. Although there are still many unanswered questions regarding fibromyalgia and its management, what has been found is that exercise is important for patients with fibromyalgia so that their quality of life can be improved. If patients with fibromyalgia do not participate in any exercises, their condition may actually deteriorate. Despite the fact that health professionals involved in the management of fibromyalgia teach patients the importance of exercises; many patients with fibromyalgia still do not want to do any form of exercises. We therefore need to find ways to help people with fibromyalgia to overcome these fears. But before we can do this we first need to find out how much different patients with fibromyalgia think when compared to healthy people when they see pictures of exercise activities.

In this study we want to find out how you react to exercises when you see pictures of others doing exercises.

Why have you been invited to participate?

You have been invited to participate in this project because you are healthy and you do not have Fibromyalgia.

What will your responsibilities be?

Your responsibilities will be to firstly ensure that you understand the purpose of this project and that the information you provide is the truth.

Will you benefit from taking part in this research?

Your participation in this project will help future research, health professionals and especially fibromyalgia patients.

Are there in risks involved in your taking part in this research?

For this part of the project there are no risks involved in you participating.

If you do not agree to take part, what alternatives do you have?

There will be no negative consequences if you do not agree to participate in this project. You may also ask the researchers for more information regarding your condition and what other treatment options are available for you.

Who will have access to your medical records?

The only people that will have access to your information are the people directly involved in the study and myself. The information collected will be treated as private and will be protected from others who should not see them. When the data is printed in the study thesis and is published, your name or details will not appear in the paper and there will be no indication that it was your information.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

The principal researcher is currently registered with the Health Professionals Council of South Africa as a private physiotherapist, and is also privately insured for malpractice and public liability by the South African Society of Physiotherapy. The insurance policy provides indemnity for all cases arising during professional duties; be it in the private or public sector. The insurance policy also indemnifies the insurer (the researcher in this case) against claims arising during the participation of the public in research projects. Therefore, in the unlikely event of an injury occurring during your participation in this research project, the insurance policy will cover all related costs and expenses incurred by you and the researcher.

Will you be paid to take part in this study and are there any costs involved?

No, you will not be paid to take part in the study, but your transport will be covered for each visit, to and from the study venue. There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

You should inform your family practitioner or usual doctor that you are taking part in a research study.

You can contact Linzette Morris on 0828652261 if you have any further queries or encounter any problems.

You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..…….. agree to take part in a research study entitled:

Virtual reality exposure therapy as treatment for pain catastrophizing in Fibromyalgia patients: Proof-of-concept

I declare that:

I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered.

I understand that taking part in this study is voluntary and I have not been pressurised to take part.

I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2010.

.....…..…….. .....…..……..

Signature of investigator Signature of witness

Declaration by investigator

I *(name)* ……..…… declare that:

I explained the information in this document to ……..

I encouraged him/her to ask questions and took adequate time to answer them.

I am satisfied that he/she adequately understands all aspects of the research, as discussed above

I did/did not use an interpreter. (If an interpreter is used then the interpreter must sign the declaration below.

Signed at (*place*) .....…….. on (*date*) ……...…….. 2010.

.....…….. .....……..

Signature of investigator Signature of witness

Declaration by interpreter

I *(name)* ……..…… declare that:

I assisted the investigator (name) …….. to explain the information in this document to (name of participant) ……..…….. using the language medium of Afrikaans/Xhosa.

We encouraged him/her to ask questions and took adequate time to answer them.

I conveyed a factually correct version of what was related to me.

I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…….. on (*date*) ……...……..2010

.....…….. .....……..

Signature of investigator Signature of witness

APPENDIX 11: Form for focus group

Study ID no: _____

Visual	What do you think is being represented in the picture?	When you look at the picture what do you think/how do you feel? Please tick box which best describes how you feel/what you think of?					Do you associate the picture with anything that has happened in your life? Briefly explain the event/experience.
1		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
2		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
3		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
4		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
5		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
6		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
7		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
8		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
9		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
10		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
11		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	
12  22		Happy thoughts	Peaceful /Soothing thoughts	Feel/think nothing	Think of pain	Feel sad/depressed	

APPENDIX 12: Post-treatment survey

Participant reference number/study ID: _____

Date of initial session: ___/____/20___ **Date of final session: ___/_____/20___**

Researcher to document

Any adverse effects reported or observed? Yes / No. If yes, please explain below:

_____

_____

Post-treatment (Following final session, the subject will be asked the following questions):

EASE OF USE: Was the apparatus/ procedures easy to use and understand? YES/NO.

Explain if no:_____

_____

ACCEPTABILITY: Would you be willing to accept such a method as treatment for your condition if presented in Tygerberg Hospital? YES/NO.

Explain if no:_____

_____

Duration of sessions/intervention: Was the duration/length of the sessions appropriate? Was the duration/length of the intervention appropriate? YES/NO

Explain if no:_____

_____

APPENDIX 13: Permission granted to conduct of study at TBH Rheumatology Clinic (email)

From: Manie, M, Dr <mou@sun.ac.za>
Sent: 29 June 2010 02:44 PM
To: Morris, LD, Ms <ldmorris@sun.ac.za>
Cc: Du Toit, R, Dr <rdutoit@sun.ac.za>
Subject: RE:

Linzette,

You have our approval and blessing to proceed with the study on patients at our Rheumatology Clinic with fibromyalgia.

Kind regards,

Mou

Dr M Manie
Division Rheumatology
Tygerberg Hospital/Faculty of Health Sciences,University of Stellenbosch;Francie Van Zijl Avenue;Parow 7505
Fax : 021- 9317442
Phone : 021-9389682 or 021- 9384944

-----Original Message-----
From: Morris, LD, Ms <ldmorris@sun.ac.za>
Sent: 28 June 2010 20:35 PM
To: Manie, M, Dr <mou@sun.ac.za>
Subject: FW:

Dear Dr Mou Manie,

Trust you are well.

Regarding the Fibromyalgia and Virtual reality exposure therapy study we liaised about earlier this year, I would now need to kindly ask you if you would give me permission to conduct the study in the TBH Rheumatology clinic. Please review the proposal and letter I sent you with this regards.

Kind regards,

Linzette Deidré Morris (BSc Physiotherapy (UWC), MSc Physiotherapy cum laude (US)

APPENDIX 14: Permission granted to conduct of study at TBH and TBH Occupational therapy department:

DEPARTMENT of HEALTH
Provincial Government of the Western Cape

Tygerberg Academic Hospital and
Mitchells Plain & Tygerberg Oral Health Centres

dierasmu@pgwc.gov.za
tel: +27 21 938-4136 / fax: +27 21 938-4890
Private Bag X3, Tygerberg, 7505
www.capegateway.gov.za

ENQUIRIES: Dr D S Erasmus

Dear Ms L D Morris

PERMISSION TO CONDUCT YOUR RESEARCH/CLINICAL TRIAL AT TYGERBERG HOSPITAL

Virtual reality exposure therapy as treatment for pain catastrophizing in fibromyalgia pts : A proof-of-concept study

In accordance with the Provincial Research policy and Tygerberg Hospital Notice No. 40/2009, permission is hereby granted for you to conduct the above-mentioned research/clinical trial here at Tygerberg Hospital.

~~[Acting]~~ CHIEF DIRECTOR
[c:mydoc-navorsing/morris]

Date : 02 SEP 2010

The Afrikaans or Xhosa version of this document is available on request.

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